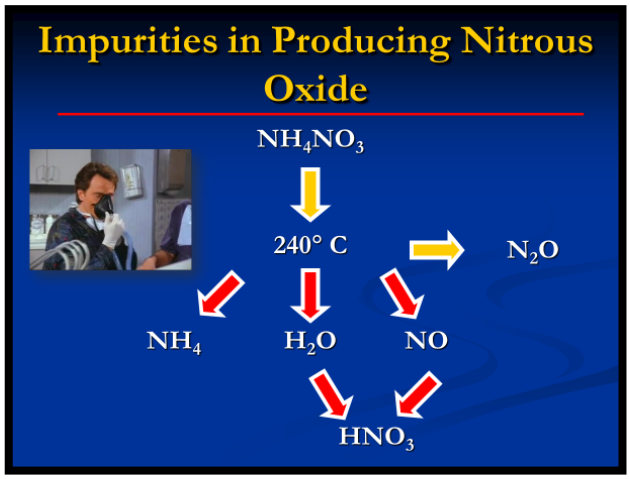
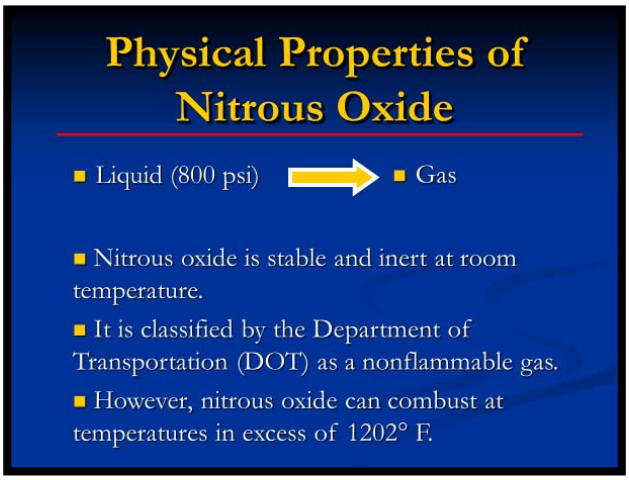
Nitrous Oxide: Pharmacology, Signs/Symptoms, Patient Selection

Characteristics of Oxygen	Characteristics of Nitrous Oxide
Clear	Clear
Colorless	Colorless
Tasteless	Tasteless (to most)
Odorless	Odorless
Produced by fractional distillation of air	Produced by careful heating of ammonium nitrate, which decomposes into nitrous oxide and water vapor.





An interesting Note: Another use for nitrous oxide has been as a boost for racecars.

$$2N_2O \rightarrow 2N_2 + O_2$$

As the reaction takes place in the combustion chamber of a car, 33% more gas is produced. This provides a boost to the piston and an increase in heat. Other effects: the oxygen given off accounts for more efficient combustion of fuel, the nitrogen buffers the increased cylinder pressure controlling combustion, and the latent heat of vaporization of the nitrous oxide reduces the intake pressure. The result is a dramatic increase in power and acceleration.

Other Notes or Questions to Ask:

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_____

_____

Description of Nitrous Oxide

Therapeutic Category - Sedative, Anxiolytic

Uses - To induce sedation and analgesia in the anxious dental patient, a principal adjunct to inhalation and IV general anesthesia (GA) in medical patients

Route of Administration – Inhalation

Dosage - 20 - 70% administered via nasal hood

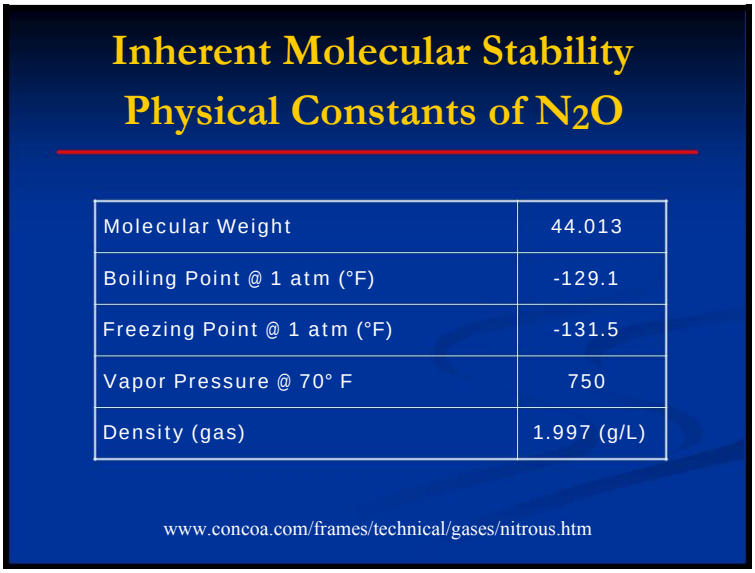
Drug Uptake - N_2O is rapidly absorbed via the lungs, onset 1-2 minutes

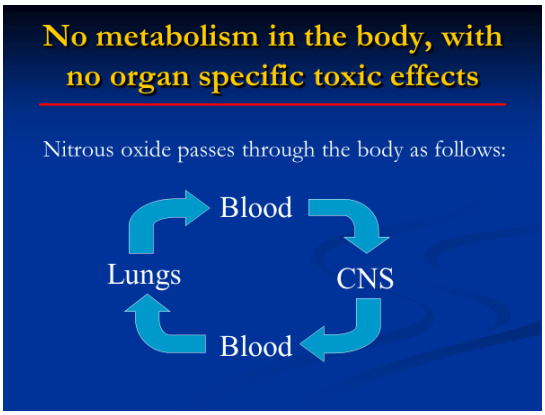
Nitrous oxide is stable and inert at room temperature -- inherent molecular stability

- Density of Nitrous oxide = 1.997 g/L
- Density of Air = 1.239 g/L

Because nitrous oxide is more dense than air, the greatest concentration of unscavenged gas will be low and near the floor.

Volatile gases move through the body based on partial pressures. The gas moves to other compartments after the first compartment is saturated.





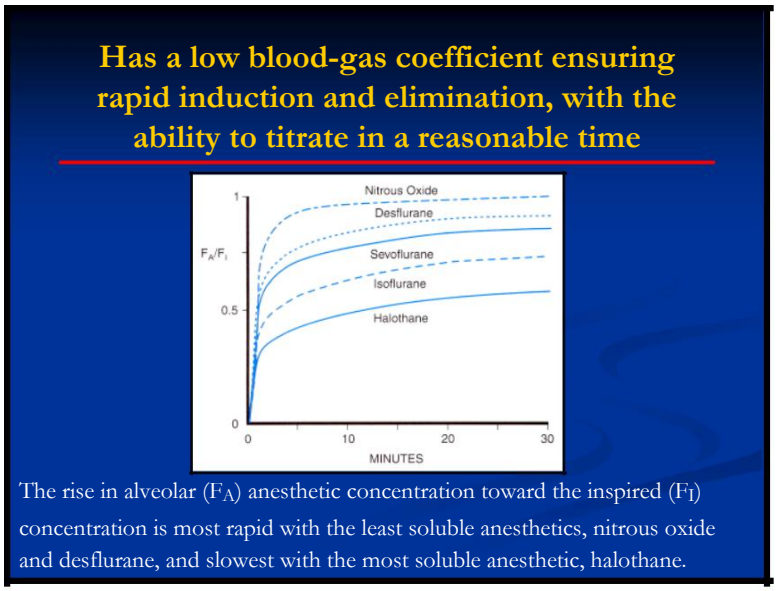
Nitrous oxide is not metabolized within the body. 99.9% of absorbed nitrous oxide is eliminated unchanged, 0.004% is recovered as metabolites After the nitrous oxide is removed delivery is stopped, the gas will diffuse back into the lungs and be exhaled unchanged: no metabolism in the body, with no organ specific toxic effects.

Other Notes or Questions to Ask:

Nitrous oxide has a low blood-gas coefficient ensuring rapid induction and elimination, with the ability to titrate in a reasonable time. The blood/gas coefficient is not related to potency but is calculated by the amount of gas needed to saturate the blood divided the amount of gas. As blood/gas coefficient increases (↑), onset of action increases (↓).

DRUGS	BLOOD/GAS	ONSET (Mins)	OIL/WATER	**MAC (%)**
N2O	0.5	1-2	1.4	103
Enflurane	1.8	3-5	98	1.7
Halothane	2.3	3-5	224	0.8
Ether	12	15-20	65	1.9
Methoxyflurane	13	15-20	970	0.2

The Minimum Alveolar Concentration (MAC) of nitrous oxide at 1 atmosphere is 103%. The MAC is a measure of anesthetic potency. The MAC is the concentration at which 50% of patients are immobile and will not respond to surgical stimuli.



Analgesic and Hypnotic Effects

- Nitrous oxide is a weak anesthetic agent
- Cannot produce surgical anesthesia under normal atmospheric conditions (MAC = 103%)
- Surgical anesthesia possible only under hyperbaric conditions
- Nitrous oxide will cause significant analgesia at concentrations as low as 20%

Nitrous oxide is sedative/hypnotic at concentrations of 30-70%. Nitrous oxide should not be given at concentrations above 70%. At concentrations >70%, an adequate amount of oxygen may not be delivered.

Other Notes or Questions to Ask:

The mechanism by which anesthetic gases produce general anesthesia is unknown. The leading theory suggests that they bind to proteins within neuronal membranes and somehow modify ion fluxes and subsequent synaptic transmission. Unlike other anesthetics, nitrous oxide produces a mild analgesic effect at subanesthetic concentrations. The mechanism for this effect most likely involves an interaction with the endogenous opioid system because it is abolished by administration of the opioid antagonist, naloxone. The strongest evidence is that nitrous oxide stimulates release of enkephalins, which bind to opioid receptors that trigger descending noradrenergic pathways. The most common estimate of analgesic efficacy suggests that 30% nitrous oxide delivered by full mask is equivalent to 10 to 15 mg morphine. This interaction with the endogenous opioid system may account in part for abuse potential attributed to nitrous oxide.

Diffusion Hypoxia (Fink Phenomenon – 1955): As nitrous oxide diffuses out of the body, it reduces the amount of oxygen within the airways, and there is a relative diffusion hypoxia. It is recommended that after the procedure is finished, that the patient be placed on 100% oxygen to help diminish this diffusion hypoxia. Diffusion hypoxia is a very rare occurrence. In fact, because the phenomenon is so rare and the chances of occurrence are further reduced by post-operative oxygen, the topic is largely academic.

Because nitrous oxide is merely absorbed and not metabolized, its effects are completely reversible with discontinuation of the nitrous oxide and/or the administration of 100% oxygen.

Ideal Signs	Ideal Symptoms	Signs of Overdose
Decreased muscle tone	Relaxation	Increased movement
Normal respiration	Light-headedness	Increased HR and BP
Peripheral vasodilation	Tingling	Increased respiratory rate
	Warmth	Increased perspiration
	Floating	Vomiting
	Euphoria	

There are some organ-specific effects within the body from nitrous oxide use to be aware of:

- Respiratory
- Cardiovascular
- CNS
- GI

Other Notes or Questions to Ask:

Respiratory Effects

Can cause direct depression of medullary ventilatory center at concentrations >50%. Decreases functional residual capacity. Relaxes bronchial smooth muscle.

Net effect = Unchanged minute ventilation and Normal $PaCO_2$

Other Respiratory Precautions:

- Presence or suspicion of pneumothorax – Nitrous oxide diffuses into air-containing spaces 34 times faster than nitrogen can diffuse out, and can lead to potentially dangerous airspace expansion, air embolus, intraocular air bubble, intracranial air bubble, middle-ear infections.

- Otitis media – specifically in children because N_2O can readily diffuse into air-filled spaces, including the middle ear. Will be very painful in this instance.

The one true contraindication to nitrous oxide:

- COPD or emphysema – Administration of N_2O may cause rupture of blebs, and/or the administration of augmented inspiratory oxygen concentrations may result in depression of ventilatory drive ("Bleb" = intrapleural air space).

Cardiovascular effects

Can cause direct myocardial depression at concentrations >40% and is a mild sympathomimetic. The overall effect on the cardiovascular system then is negligible.

CNS effects

Nitrous oxide can cause increased cerebral blood flow. It may increase intracranial pressure due to increased cerebral blood volume so caution should be exercised in:

- Head injuries – Patients with impaired level of consciousness and/or mentation should not receive nitrous oxide because cerebral blood flow and intracranial pressure could be increased.

GI effects

Nausea and vomiting are common adverse events when nitrous oxide is given at high Concentrations. It can cause intestinal rupture if administered to patient with bowel obstruction or abdominal distension although this is very rare.

Other Notes or Questions to Ask:

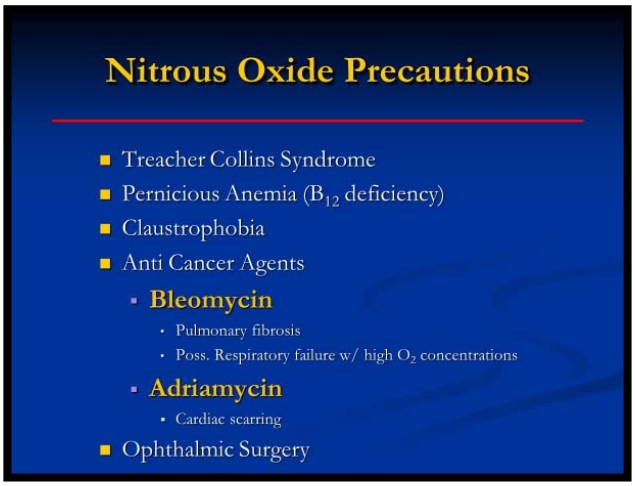
Pregnancy?

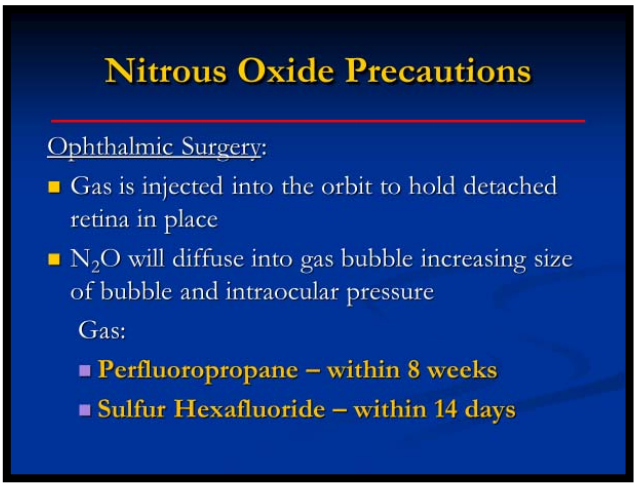
There is no evidence of fetotoxic effects with low-dose, short-term exposure. Chronic exposure (≥5 hours/day without a scavenging unit) have proven to be teratogenic resulting in spontaneous abortion, low birth weights, fetal abnormalities, and low conception rates for prospective mothers and fathers.

Rowland AS, et al. Nitrous oxide and spontaneous abortion in female dental assistants. American Journal of Epidemiology 1995;141(6):531-8.

Scuba diving within the last 24 hours

N_2O should not be used on patients who have been scuba diving in the last 24 hours to avoid decompression sickness.





Nitrous Oxide Side Effects	
Middle ear pressure	Perspiration
Abdominal Swelling	Sexual aberrations
Flatulence	Trace contamination
Vasodilation	

Other Notes or Questions to Ask:

Methylene tetrahydrofolate reductase (MTHFR) is the rate-limiting enzyme in the methyl cycle, and it is encoded by the MTHFR gene.

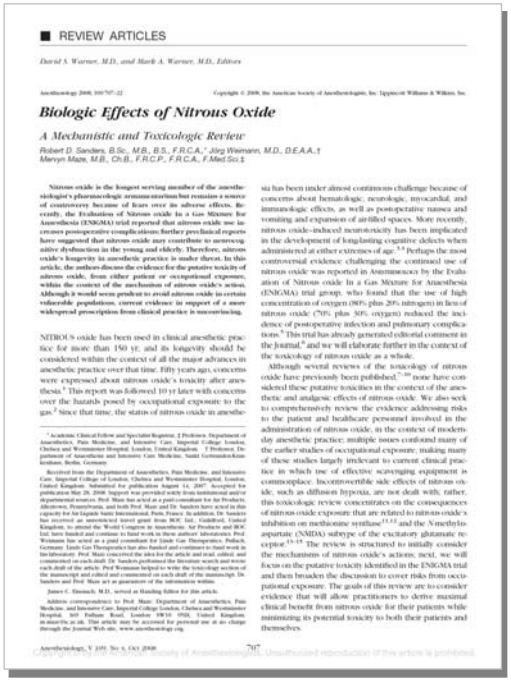
The MTHFR gene provides instructions for making an enzyme called methylenetetrahydrofolate reductase. This enzyme plays a role in processing amino acids, the building blocks of proteins.

Methylenetetrahydrofolate reductase is important for a chemical reaction involving forms of the vitamin folate (also called vitamin B9). Specifically, this enzyme converts a molecule called 5,10-methylenetetrahydrofolate to a molecule called 5-methyltetrahydrofolate.

This reaction is required for the multistep process that converts the amino acid homocysteine to another amino acid, methionine. The body uses methionine to make proteins and other important compounds

Natural variation in this gene is common in healthy people. Although some variants have been reported to influence susceptibility to occlusive vascular disease, neural tube defects, Alzheimer's disease and other forms of dementia, colon cancer, and acute leukemia, findings from small early studies have not been reproduced.

Some mutations in this gene are associated with methylenetetrahydrofolate reductase deficiency. In addition, the aberrant promoter hypermethylation of this gene is associated with male infertility and recurrent spontaneous abortion.


■ REVIEW ARTICLES

David S. Warner, M.D., and Mark A. Warner, M.D., Editors

Biologic Effects of Nitrous Oxide

A Mechanistic and Toxicologic Review

Robert D. Sanders, B.Sc., M.B., B.S., F.R.C.A.,* Jörg Weimann, M.D., D.E.A.A.,† Mervyn Maze, M.B., Ch.B., F.R.C.P., F.R.C.A., F.Med.Sci.‡

Nitrous oxide is the longest serving member of the anesthesiologist's pharmacologic armamentarium but remains a source of controversy because of fears over its adverse effects. Recently, the Evaluation of Nitrous oxide In a Gas Mixture for Anaesthesia (ENIGMA) trial reported that nitrous oxide use increases postoperative complications; further preclinical reports have suggested that nitrous oxide may contribute to neurocognitive dysfunction in the young and elderly. Therefore, nitrous oxide's longevity in anesthetic practice is under threat. In this article, the authors discuss the evidence for the putative toxicity of nitrous oxide, from either patient or occupational exposure, within the context of the mechanism of nitrous oxide's action. Although it would seem prudent to avoid nitrous oxide in certain vulnerable populations, current evidence in support of a more widespread proscription from clinical practice is unconvincing.

NITROUS oxide has been used in clinical anesthetic practice for more than 150 yr, and its longevity should be considered within the context of all the major advances in anesthetic practice over that time. Fifty years ago, concerns were expressed about nitrous oxide's toxicity after anesthesia.[1] This report was followed 10 yr later with concerns over the hazards posed by occupational exposure to the gas.[2] Since that time, the status of nitrous oxide in anesthesia has been under almost continuous challenge because of concerns about hematologic, neurologic, myocardial, and immunologic effects, as well as postoperative nausea and vomiting and expansion of air-filled spaces. More recently, nitrous oxide–induced neurotoxicity has been implicated in the development of long-lasting cognitive defects when administered at either extremes of age.[3,4] Perhaps the most controversial evidence challenging the continued use of nitrous oxide was reported in Anesthesiology by the Evaluation of Nitrous oxide In a Gas Mixture for Anaesthesia (ENIGMA) trial group, who found that the use of high concentration of oxygen (80% plus 20% nitrogen) in lieu of nitrous oxide (70% plus 30% oxygen) reduced the incidence of postoperative infection and pulmonary complications.[5] This trial has already generated editorial comment in the Journal,[6] and we will elaborate further in the context of the toxicology of nitrous oxide as a whole.

Although several reviews of the toxicology of nitrous oxide have previously been published,[7–10] none have considered these putative toxicities in the context of the anesthetic and analgesic effects of nitrous oxide. We also seek to comprehensively review the evidence addressing risks to the patient and healthcare personnel involved in the administration of nitrous oxide, in the context of modern-day anesthetic practice; multiple issues confound many of the earlier studies of occupational exposure, making many of these studies largely irrelevant to current clinical practice in which use of effective scavenging equipment is commonplace. Incontrovertible side effects of nitrous oxide, such as diffusion hypoxia, are not dealt with; rather, this toxicologic review concentrates on the consequences of nitrous oxide exposure that are related to nitrous oxide's inhibition on methionine synthase,[11,12] and the *N*-methyl-D-aspartate (NMDA) subtype of the excitatory glutamate receptor.[13–15] The review is structured to initially consider the mechanisms of nitrous oxide's actions; next, we will focus on the putative toxicity identified in the ENIGMA trial and then broaden the discussion to cover risks from occupational exposure. The goals of this review are to consider evidence that will allow practitioners to derive maximal clinical benefit from nitrous oxide for their patients while minimizing its potential toxicity to both their patients and themselves.

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Bottom Line:

Nitrous oxide & oxygen should be used with caution in patients with MTHFR deficiency (one or more of the C667T variant or a combination of the C677T + A1298C).

Prophylactic use of Vitamin B12 and Folic acid can blunt the nitrous oxide-induced increase in plasma homocysteine. (Ref: Anesthesiology 2013;119(1):19-28.

Other Notes or Questions to Ask:

Nitrous Oxide
Contamination and Scavenging

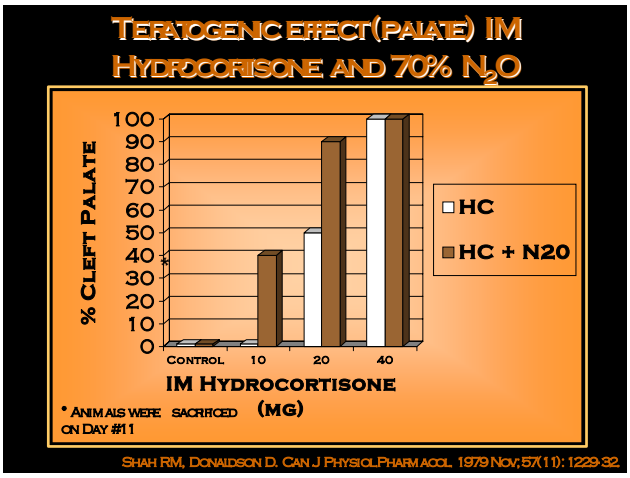
Introduction to potential health hazards of trace anesthetics and proposed techniques for limiting occupational exposure.

Animal Studies

Several studies have examined the effects of nitrous oxide on the development of animal embryos with inconsistent results. Discrepancies between these conclusions are due to:

- Different animals
- Different gas concentrations
- Different times during pregnancy of exposure
- Different durations of exposure

Mutagenicity tests of other inhalational anesthetics have also provided no evidence of carcinogenicity or organ toxicity, although some animal studies indicated that chronic exposure to nitrous oxide concentrations of 1000 ppm or higher can result in teratogenicity.



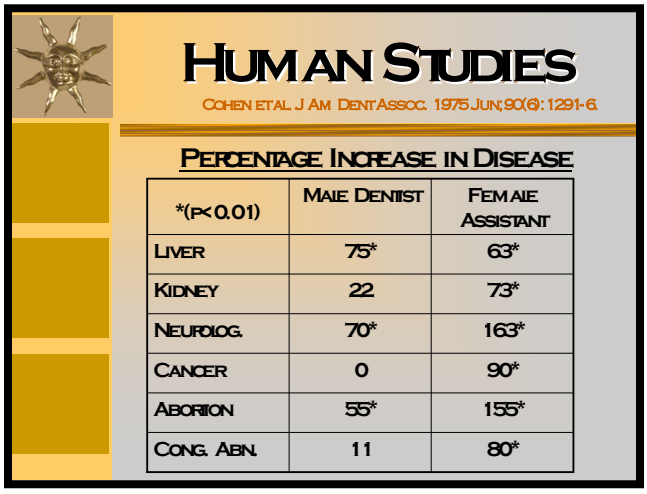
Human Studies

Cohen 1975: Retrospective Questionnaire defined Levels of Exposure as:

0	None
1-2999 hours	Light
≥ 3000 Hours	Heavy

Return Rate: 70%

Dentists: 21,000/120,000
Assistants: 22,000/150,000



Epidemiological Errors:

- ☑ Retrospective
- ☑ Inadequate Control
- ☑ Incomplete Return
- ☑ Biased Return
- ☑ Unknown Exposure
- ☑ Unsupported by other studies
- ☑ unsupported Diagnosis of defect

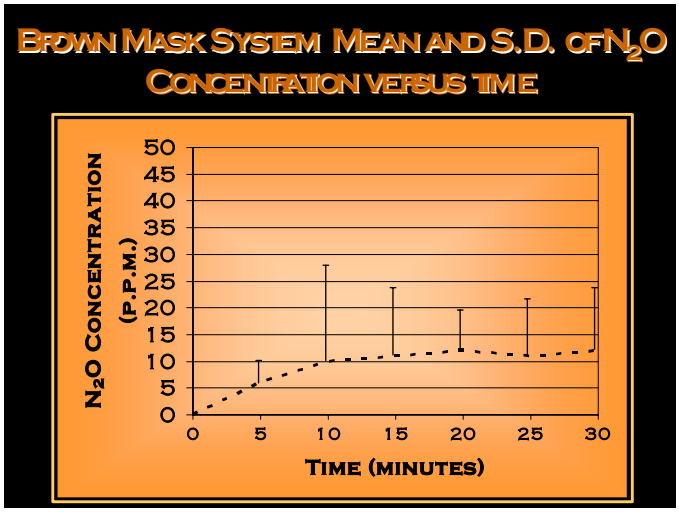
Other Notes or Questions to Ask:

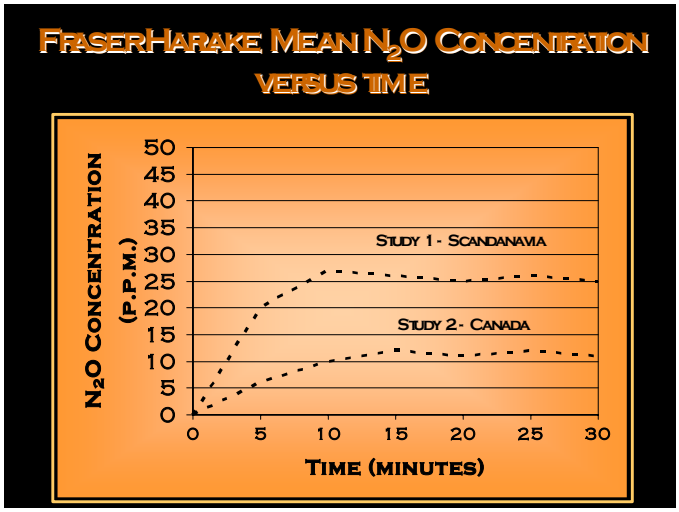
Cohen 1980 (Heavily Exposed is redefined as >8 hours per week):

Heavily Exposed Dentist		Female Assistants Exposed	
1.7	fold increase in liver disease	1.6	fold increase in liver disease
1.2	fold increase in kidney disease	1.7	fold increase in kidney disease
1.9	fold increase in neurological disease	2.8	fold increase in neurological disease
1.5	fold increase in spontaneous abortions in wives	2.3	fold increase in spontaneous abortions in wives
		1.5	fold increase in Cancer Rates

N_20 Contamination Factors

1.	Movement	48%
2.	Talking	46%
3.	Mask Leakage	17%
4.	Poor Suction	13%
5.	Laughing	11%
6.	Mouth Breathing	7%
7.	Moustache	5%





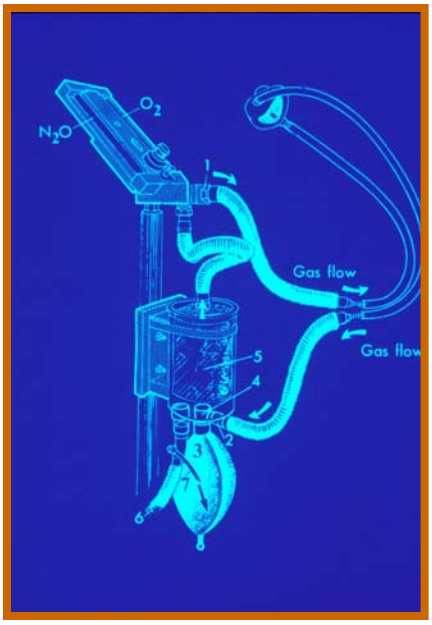
Comparison of the Tested Masks

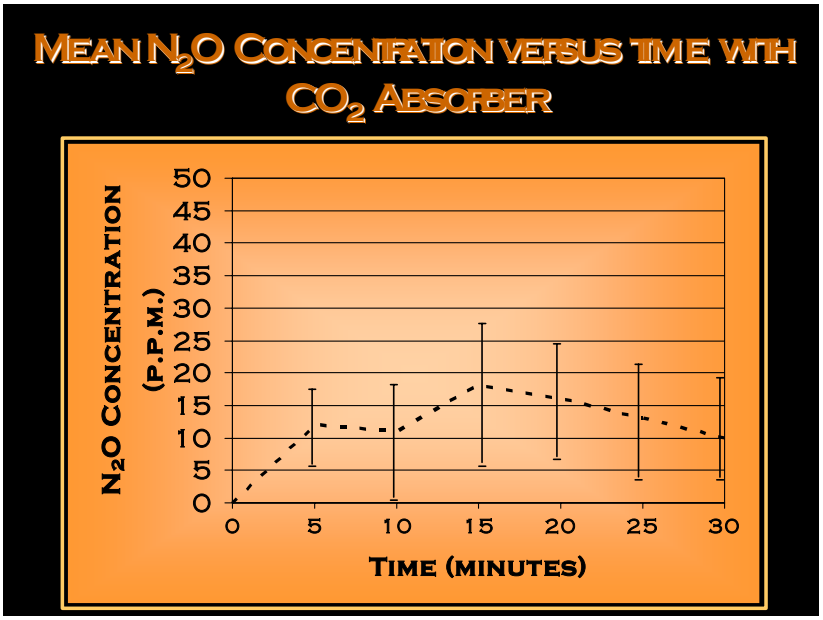
N	Mask Type	Mean ppm N2O
35	Brown	43.4
29	Porter	48.2
24	Parkell	54.4
23	Dupaco	61.2
33	Fraser- Harlake	62.7

Other Notes or Questions to Ask:

Carbon Dioxide Absorber

How can we minimize occupational exposure?





Tomaszewski L, Nadworny J, Zmudzka B. Vitamin B-12 and sterility. Pol Tyg Lek. 1964 Dec 14;19:1915-8.

↑ Vit B12 = increases human sperm motility
↓ Vit B12 = increases human infertility

Shah NK, Kripke BJ, Sanzone CF, Cosman EB. Histological evaluation of cutaneous wound healing in presence of nitrous oxide in rats. Anesth Analg. 1978 Sep-Oct;57(5):527-33.

Effect of 20% N_2O on rat spermatogenesis after 5-week exposure:
Decreased sperm count
Abnormal multinucleated giant cells
Total recovery after 3 days

Volchansky A, Viera E. Some extrinsic factors in the aetiology of periodontal disease I. J Dent Assoc S Afr. 1983 Mar;38(3):192-5.

"Concentrations at which there were no longer significant effects of nitrous oxide on rat litter size over a 10-day exposure period were between 3250-3500 ppm"

Brodsky JB, Baden JM, Serra M, Kundomal Y. Nitrous oxide inactivates methionine synthetase activity in rat testis. Anesthesiology. 1984 Jul;61(1):66-8.

Effect of N2O on rat testicular methionine synthetase activity after 1 hour exposure

Level	Exposure	Reduction	Recovery
10%	1 hour	29%	48 hours
50%	1 hour	63%	72 hours

Other Notes or Questions to Ask:

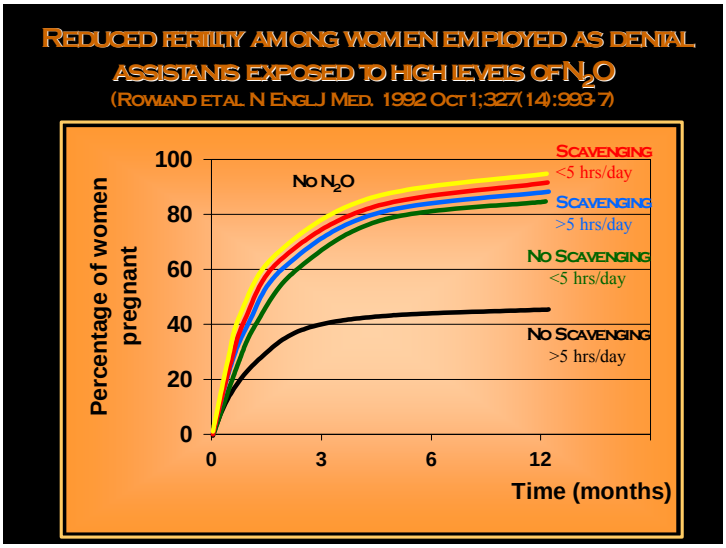
Sweeney B, Bingham RM, Amos RJ, Petty AC, Cole PV. Toxicity of bone marrow in dentists exposed to nitrous oxide. Br Med J (Clin Res Ed). 1985 Aug 31;291(6495):567-9.

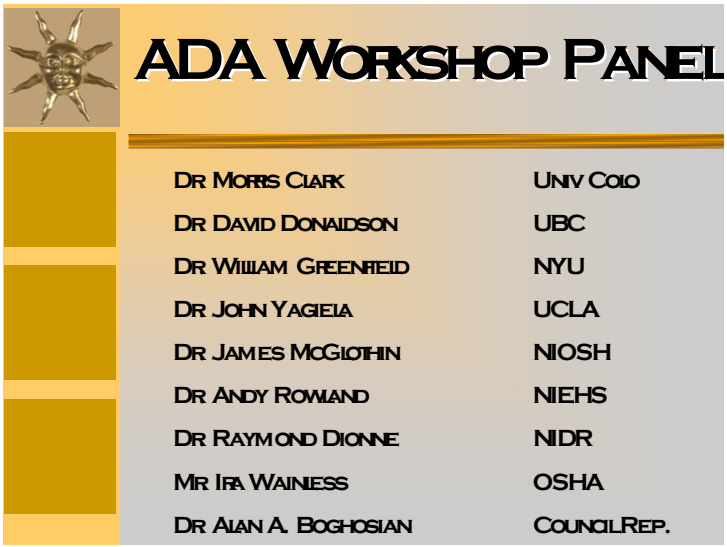
- Deoxyuridine suppression test on dentists using nitrous oxide suggest 400 ppm as a safe level
- Provided the first direct evidence that occupational exposure to N_2O can result in altered vitamin B_{12} metabolism and impaired synthesis of methionine synthase (a crucialenzyme for DNA formation)

Yagiela JA. Health hazards and nitrous oxide: a time for reappraisal. Anesth Prog. 1991 Jan-Feb;38(1):1-11.

- Evidence is overwhelming that prolonged exposure to clinical concentrations of N2O inhibits cellular proliferation of the formed elements of the blood and can lead to megaloblastic anemia, leukopenia and thrombocytopenia.
- A time-weighted average of 100ppm for an eight-hour workday and/or a time-weighted average of 400ppm per anesthetic administration would provide adequate protection of dental personnel.

ADA guidelines are 50 ppm TWA for offices, 25ppm TWA for hospital settings





ADA Workshop Panel Conclusions

1. N2O/O2 is a very valuable tool for pain and anxiety control and it should continue to be taught at all levels of dental education.
2. Chronic occupational exposure to N2O/O2 in offices without scavenging units may be associated with deleterious neurological and reproductive effects on the health of dental personnel.
3. Where scavenging systems are used there has been no such evidence to date. Appropriate scavenging systems and methods of administration should be adopted.
4. It should be clearly indicated that potential health hazards of N2O do not apply to the patient.
5. N2O levels vary significantly among offices using scavenging systems. Therefore a protocol should be implemented.
6. State dental boards regulate certification programs requiring evidence of satisfactory completion of educational programs.

Other Notes or Questions to Ask:

Recommended Checklists

On Installation	- Whole system (spectrophotometer)
Daily	- Rubber hoses - Nasal masks - Connectors (high and low pressure) - Reservoir bags (visual)
Quarterly	- Whole system (spectrophotometer)

References and Recommended Reading for Medications for Nitrous Oxide Contamination & Scavenging

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Other Notes or Questions to Ask:

Myth #1: "My Dentist Still Uses Novocain"

We all know this myth is totally BUSTED, but let's briefly look back at the history of Novocain… by the way there is no "e" in Novocain (the brand name for procaine)

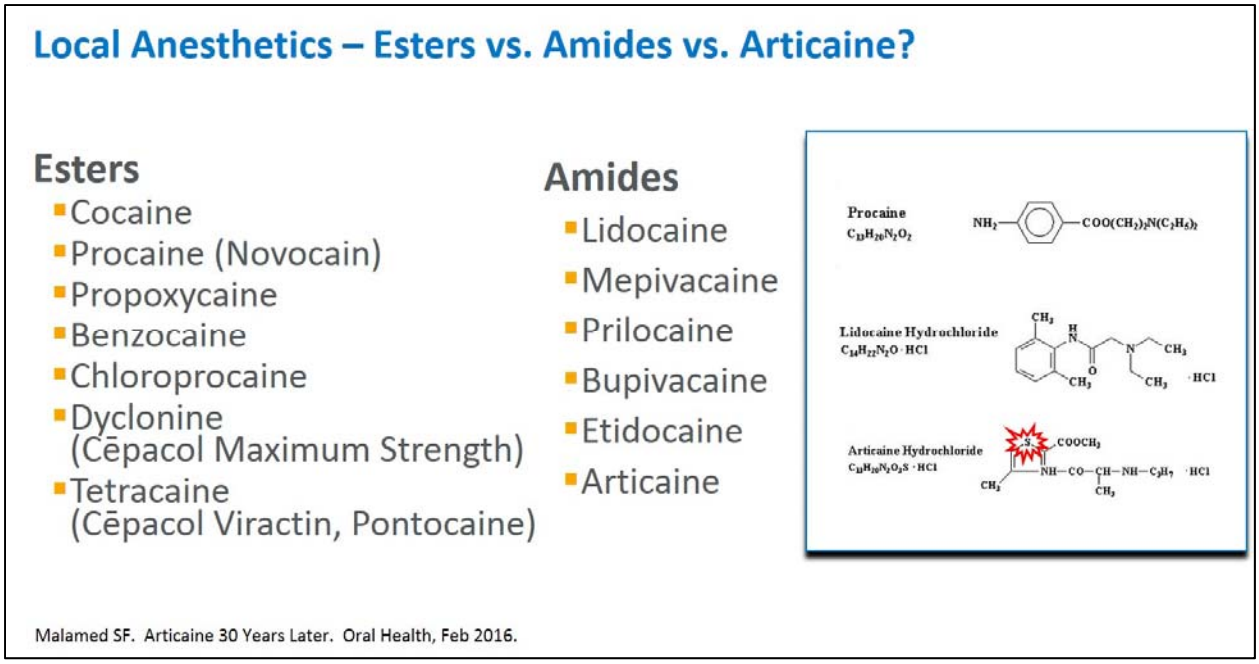
Historical Perspective

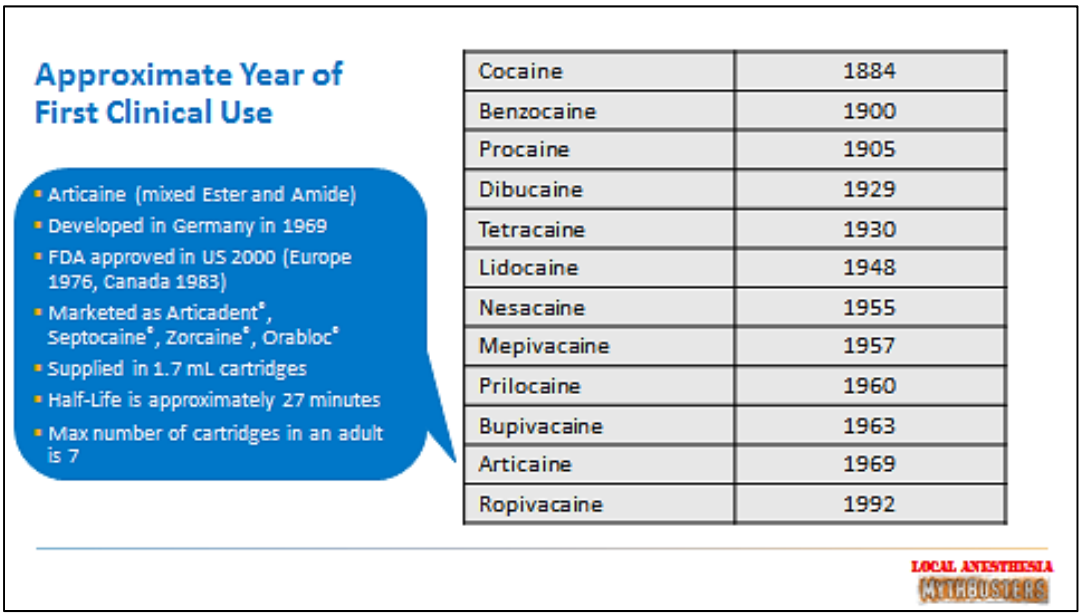
- The first local anesthetic was Cocaine
- Carl Koller (September 1884) used cocaine as a local anesthetic during a surgical procedure (for glaucoma)
- "The facts are that neither Freud nor I discovered that cocaine is a local anesthetic. This was discovered by Dr. Albert Niemann, who extracted the potent principle from coca leaves in 1860" ~ Dr. Koller (*JAMA* 1941;117(15)1284.)
- Dr. Koller was nominated for the Nobel Prize several times but never received it, mostly because his discovery was made 17 years before the Nobel Prize was created. (www.dentaleconomics.com/articles/print/volume-89/issue-3/features/the-story-of-local-anesthesia.htm)
- William Halsted (November 1884) developed the principles of nerve block using Cocaine
- Infraorbital and IA blocks were performed on him as a "guinea pig" it took him 3 years to overcome his resulting Cocaine addiction (*Ann Surg* 1997 May;225(5):445-58.)
- Due to the unfavorable therapeutic index of Cocaine the search was on for a less toxic compound with LA properties:
  1904 – Alfred Einhorn synthesized the ester Procaine (Novocain)
  1943 – Nils Lofgren synthesized Lidocaine which possessed:
  - Less allergenicity
  - More potency
  - More rapid onset of action
  - First brand name = Xylocaine (Astra Pharmaceutical)

  2000 – Articaine granted FDA approval in the US
  2008 – OraVerse (phentolamine mesylate) approved

A little more info on Procaine…

- First synthetic injectable local anesthesia used in dentistry
- Produced the greatest amount of vasodilation of all currently used local anesthetics
- Ester type – capable of allergy - PABA
- pKa=9.1, slow onset (6-10 minutes) and at physiologic pH existed as 90% charged (inactive) and 10% uncharged (active)
- Duration of action (epinephrine can be added to prolong action)
- Pulpal anesthesia (mx infiltration) lasts about 5 minutes
- Soft tissue anesthesia lasts for approximately 30 minutes
- Blocks are not recommended (slow onset, ultra short duration)
- Systemic toxicity negligible because procaine is rapidly destroyed in the plasma





<u>1.7mL vs. 1.8mL on Local Anesthetic Cartridges</u>

- Average cartridge volume in U.S. is 1.76mL (*JADA* 2007;138:1104–1112.)
- During the approval process for Articaine in the 1990's the FDA asked the manufacturer, "Can you guarantee that each and every cartridge contains at least 1.8mL of solution?" the answer was "No." (Malamed SF. Clinical Action of Specific Agents. In: Handbook of Local Anesthesia. 6th Edition. 2014. p 56.)
- Therefore, manufacturers began printing a volume of 1.7mL on the cartridges

Lots of Brand Names for local anesthetic solutions…

- Retail costs for local anesthetics $30-50
- Exception is Bupivacaine ~$60

Myth #2: "Doctor, I'm allergic to epinephrine!"

Again, we know this myth is BUSTED, but this is such a common patient report that is worth looking into!

Pharmacokinetics of Epinephrine

- Naturally occurring
- It is on the World Health Organization's List of Essential Medicines, the most important medications needed in a basic health system
- Onset of action: 1-2 minutes
- Duration of action: 1-2 minutes
- Acts directly on alpha and beta adrenergic receptors (50:50, alpha constricts and beta dilates)
- Antagonizes the effects of histamine
- Stimulates the liver to produce and raise blood glucose levels
- Increases HR, cardiac contractility, and systemic vascular resistance
- Increases myocardial oxygen demand

Epinephrine – Historical Progression

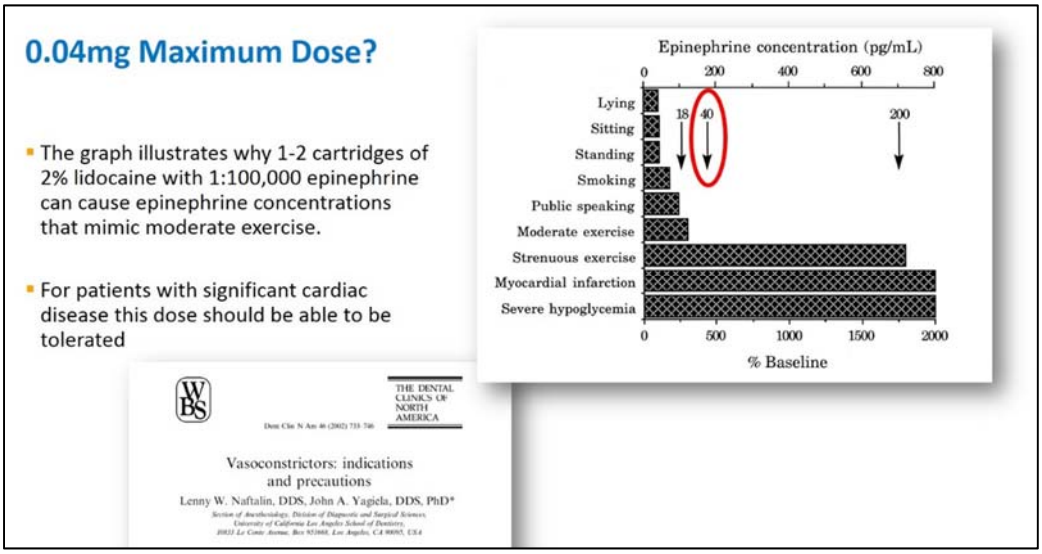
- In 1986, the AHA emphasized safety by concluding, "Vasoconstrictor agents should be used in local anesthesia solutions during dental practice only when it is clear that the procedure will be shortened or the analgesia rendered more profound. When a vasoconstrictor is indicated, extreme care should be taken to avoid intravascular injection. The minimum possible amount of vasoconstrictor should be used."

- Malamed and Bennet, proposed 0.04mg as a maximum dose of epinephrine for patients with severe cardiac disease

Table I. Contraindications to vasoconstrictors in dentistry

Absolute contraindications
Heart diseases
a. Unstable angina
b. Recent myocardial infarction
c. Recent coronary artery bypass surgery
d. Refractory arrhythmias
e. Untreated or uncontrolled severe hypertension
f. Untreated or uncontrolled congestive heart failure
Uncontrolled hyperthyroidism
Uncontrolled diabetes
Sulfite sensitivity; steroid-dependent asthma
Pheochromocytoma
Relative contraindications
Patients taking tricyclic antidepressants
Patients taking phenothiazine compounds
Patients taking monoamine oxidase inhibitors
Patients taking nonselective β-blockers
Cocaine abuser

References:
Dent Clin North Am 2002;46(4):733-46.
Oral Surg Oral Med Oral Pathol 1992;74:679-86.



The "Reaction"

- But what about those patients who suffer from the following symptoms after local anesthetic injection?
- Heart palpitations or racing heartbeat
- Pale, sweaty skin
- Dizziness
- Nervousness
- Headache
- Most likely to occur during IANB
- Rates of positive aspiration for IANB :
    - 5.8% in approximately 6000 injections (Ann Anat 1999;181:105-6.)
    - 8.1% in 731 injections (JADA 1999:130:496-9)
    - Other authors have suggested a wider range (2.6-30%) with factors such as needle size and anatomy playing a role (JADA 1992;123:69-73)

Technique	Needle Gauge	Needle Length
Palatal Approach (ASA)	30	Ultrashort
PSA Nerve Block	27	Short
Infiltration	27	Short
Buccal (Long) Nerve Block	27	Short
PDL Injection	27	Short
IA Nerve Block	25	Long
Gow-Gates Nerve Block	25	Long
Vazirani-Akinosi Nerve Block	25	Long

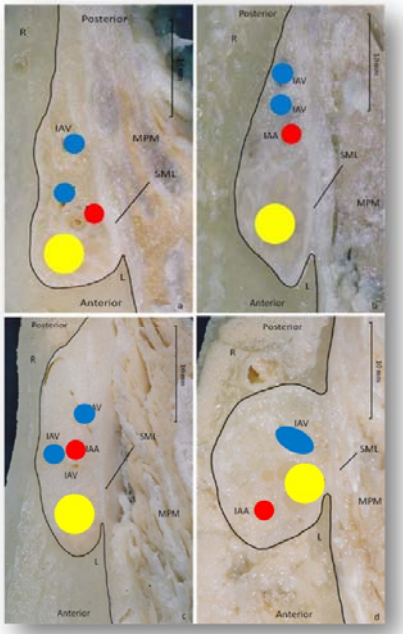
Source: Malamed SF. Handbook of Local Anesthesia. 2004, 5th Ed. p 106.

Location of the Nerve and Vessels in the Mandible

Transverse sections of the right mandibular ramus at the level of the lingula of four representative specimens

These specimens show the inferior alveolar nerve to be located posterolateral to the tip of the lingula

The location of the inferior alveolar artery and vein(s) varies significantly with the inferior alveolar artery being posterior or posterolateral



Clin Anat 2010;23:936–944.

Take home message…

"The addition of a suitable vasoconstrictor in adequate concentration increases the efficiency of local anaesthetic preparations and reduces the toxicity; their presence is therefore desirable. There is far greater danger of untoward reactions from the use of preparations without a vasoconstrictor than from the small amount of adrenaline normally present."
(*Aust Dent J* 1968 Feb;13(1):65-9.)

Recommendations:

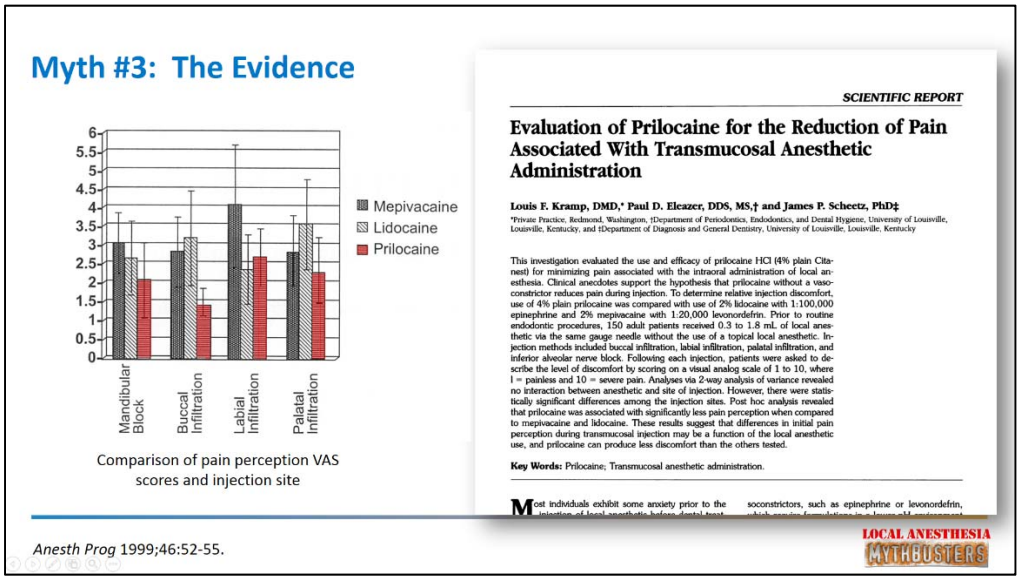
- The "Reaction" is most likely to occur during IANB in the mandible
- Use the right size needle (avoid 30ga for IANB in adults and kids) (*Dent Clin North Am* 2010;54:745–756.)
- Aspirate (twice)
- Slow injection technique – fast injection technique may cause back pressure within the vessel and decrease chances of positive aspiration (*Ann Anat* 1999;181:105-106)
- Consider reduced/no epinephrine dose formulations:
  - 4% articaine with 1:200,000 (multiple brands)
  - 4% Citanest Forte with 1:200,000 epi (Prilocaine, Dentsply Sirona)
  - 3% mepivacaine (multiple brands)
  - 4% Citanest (Prilocaine, Dentsply Sirona)
  - 2% Xylocaine (Lidocaine, Dentsply Sirona), last available 2011 in the U.S. (*Pediatr Dent* 2015 Sep-Oct;37(5):71-77)

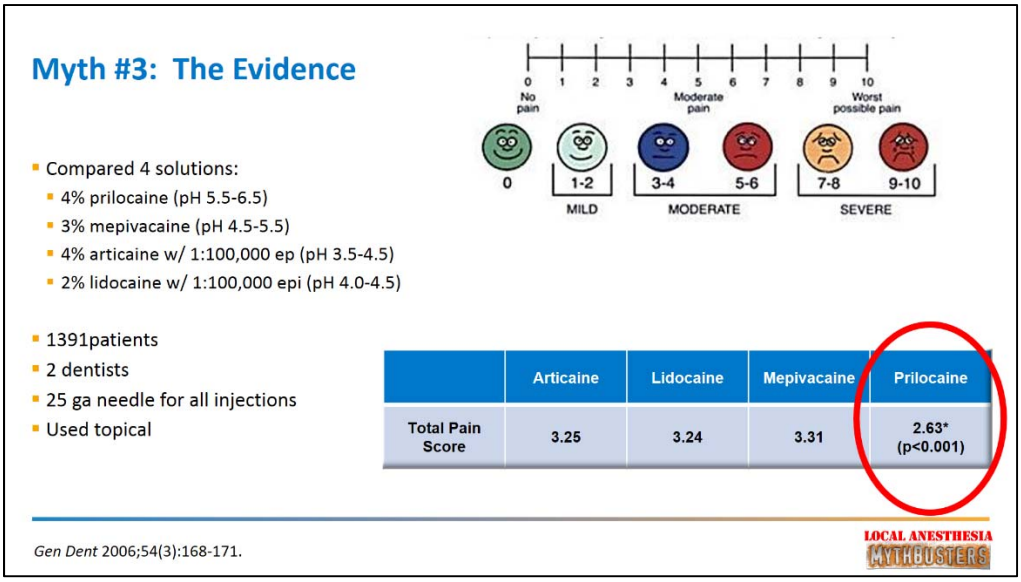
Myth #3: "First, I give a local anesthetic without epinephrine to my patients, because it stings less."

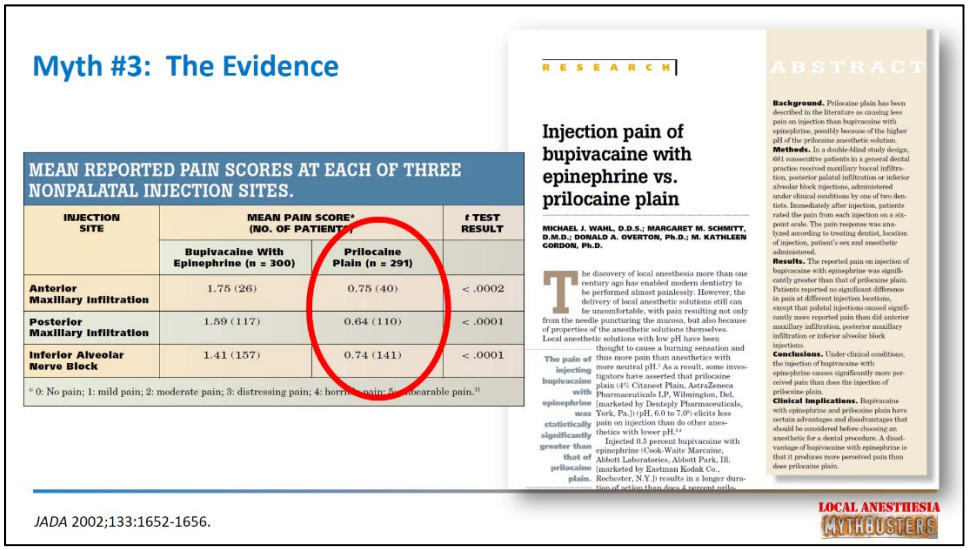
Background: Some dentists believe that by using a plain local anesthetic solution (ie, no epi) that the patient won't feel a pinch, sting, or burn at injection

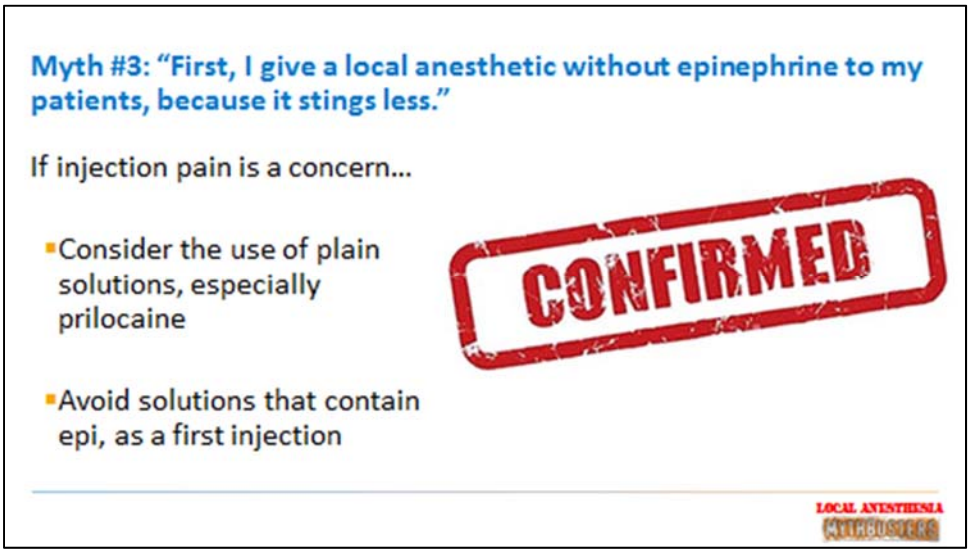
Could be related to pH. It is well-known that solutions containing a vasconstrictor (eg, epi) have a lower pH then plain solutions

Local Anesthetic Ph (Source: *Compend Contin Educ Dent* 2016 May;37(5):e6-e12.)
Average pH of solutions containing epinephrine: 3.82
Average pH of plain solutions: 6.34









One more thing… who has heard of buffering local anesthetics?

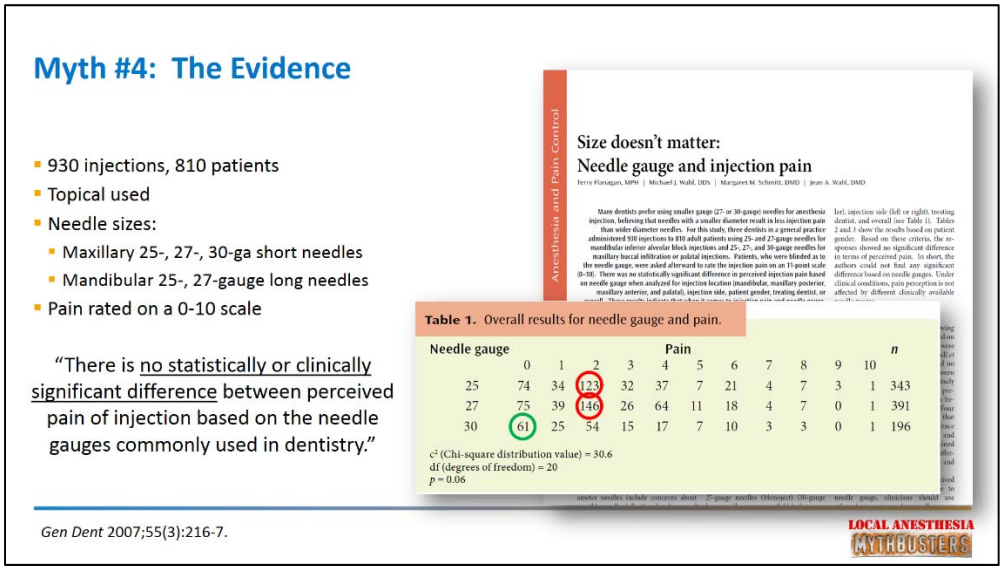
- Local anesthetic buffering involves adding Sodium Bicarbonate to low pH solutions to raise the pH closer to physiologic levels
- Possible benefits include:
- Faster onset
- Better efficacy
- Less injection pain
    - The data on whether buffering decreases injection pain is equivocal (*Gen Dent* 2015;63(6):74-78.)
    - All the studies look at buffered vs. non-buffered lidocaine or articaine
    - We need to look at buffered vs. prilocaine!

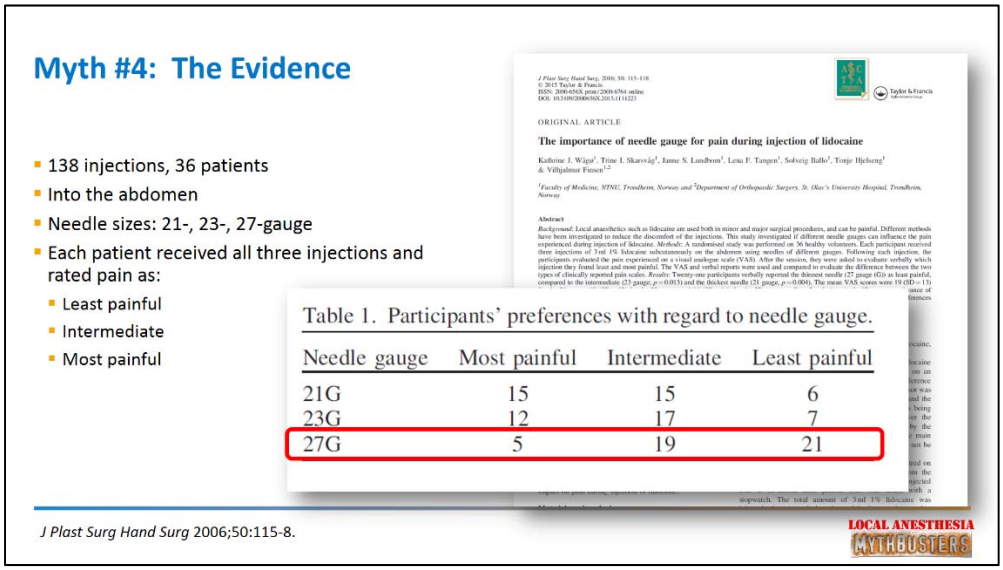
Myth #4: "I use small needles for my injections because they are less painful to the patient compared to larger needles."

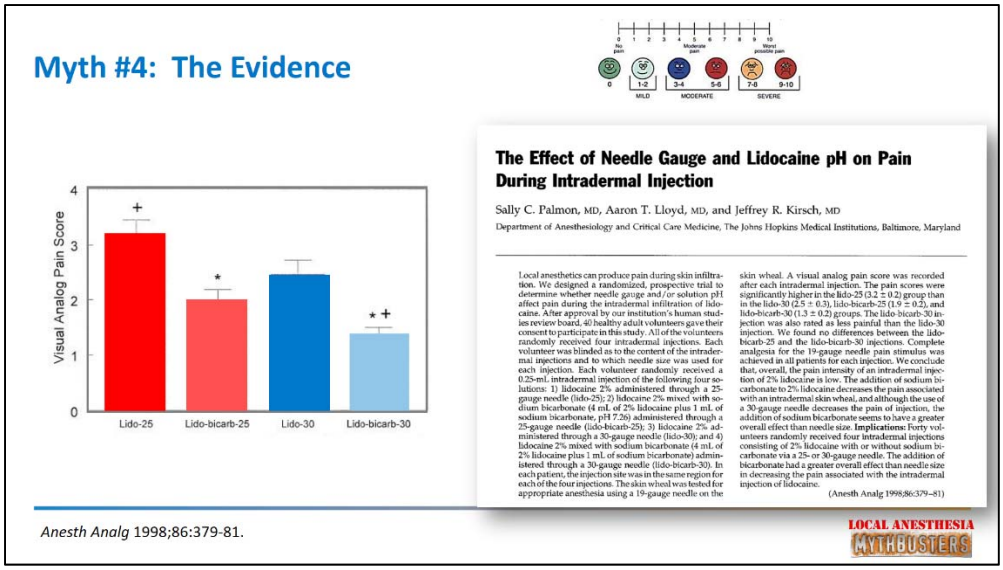
Background: There is a long-standing belief in dentistry that using a smaller gauge needle will cause less discomfort to the patient

This myth has long persisted despite some early evidence:

- "patients are unable to differentiate among 23-, 25-, 27-, and 30-gauge needles" (*NY State Dent J* 1972;38:425-426.)
- "no significant differences in the perception of pain produced by 25-, 27-,and 30-gauge needles during inferior alveolar nerve blocks in adults" (*JADA* 1979;99:822-824.)





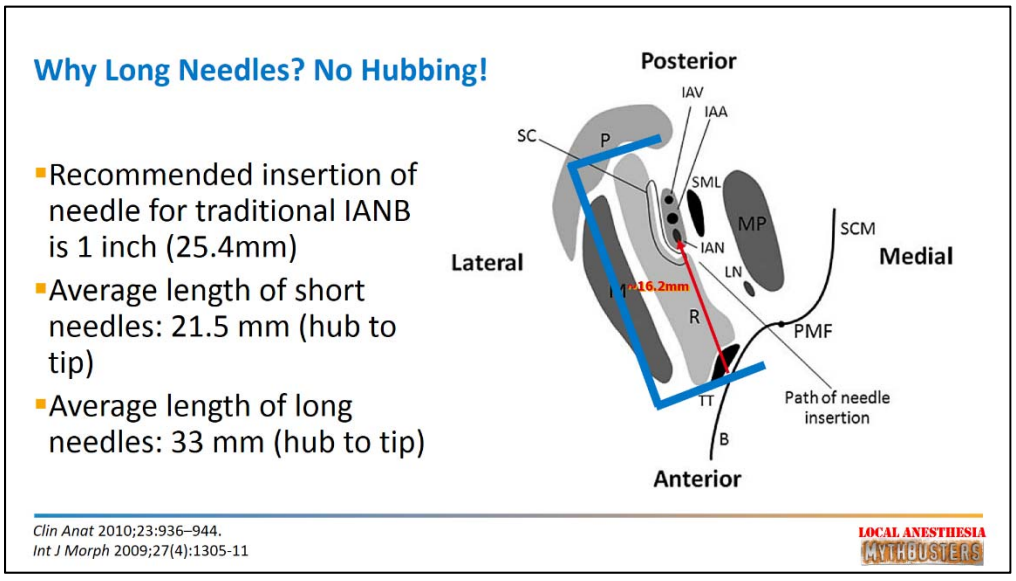


The Verdict…UNCLEAR

Recommendations

- Use the right size needles!
- Why? Not for patient comfort but for reasons such as:
  - Needle deflection
  - Ability to aspirate (less pressure required)
  - Decreased risk of breakage
- For IANB use 25- or 27-ga long needles
- For infiltrations use 27-ga (or 30-ga) short needles
- To help avoid needle breakage:
  - Minimize bending of needles
  - Minimize reorienting needles when in tissue
  - Avoid hubbing the needle

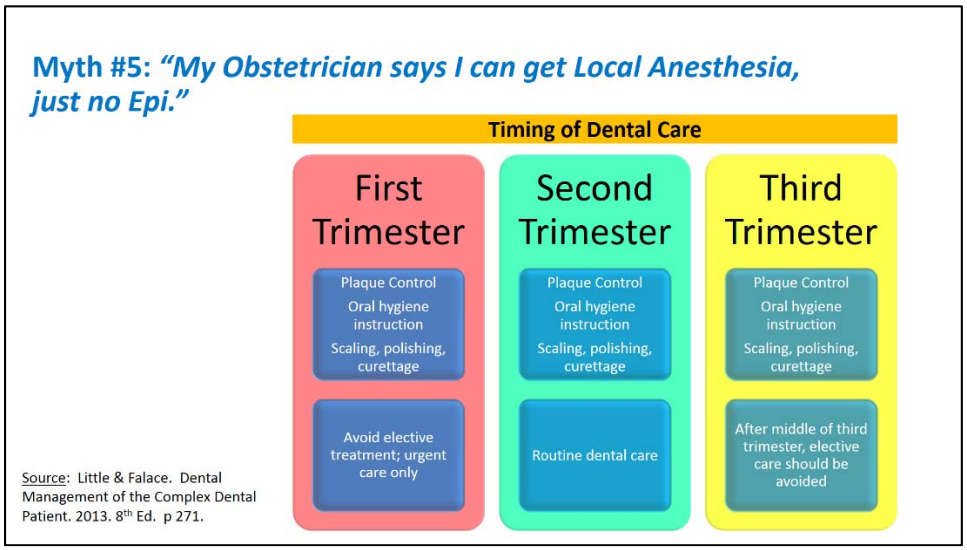
Why Long Needles? No Hubbing!



Myth #5: "My Obstetrician says I can get Local Anesthesia, just no Epi."

Changes in 2014:

- On 12/13/2014, the FDA published the Pregnancy and Lactation Labeling Final Rule (PLLR), which changed the labeling requirements for the pregnancy and lactation sections for prescription drugs and biological agents
- The final rule removed the pregnancy letter categories, and created descriptive subsections
- Labeling changes from this rule begin on June 30, 2015. Previously approved drugs from June 30, 2001 will switch to the new labeling gradually.
- This rule does not apply to OTC medications



What is a TERATOGEN?

Any agent that can disturb the development of an embryo or fetus. Teratogens may cause a birth defect in the child. Or a teratogen may halt the pregnancy outright. The classes of teratogens include radiation, maternal infections, chemicals, and drugs.

Category	FDA Pregnancy Risk Factor Definitions
A	Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of risk in later trimesters), and the possibility of fetal harm appears remote.
B	Either animal reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of risk in later trimesters).
C	Either studies in animals have revealed adverse effects on the fetus (teratogenic, embryocidal, or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.
D	There is positive evidence of human fetal risk, but the benefits of use in pregnant women may be acceptable despite the risk (for example, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
X	Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.
N	FDA has not classified the drug

The Facts:

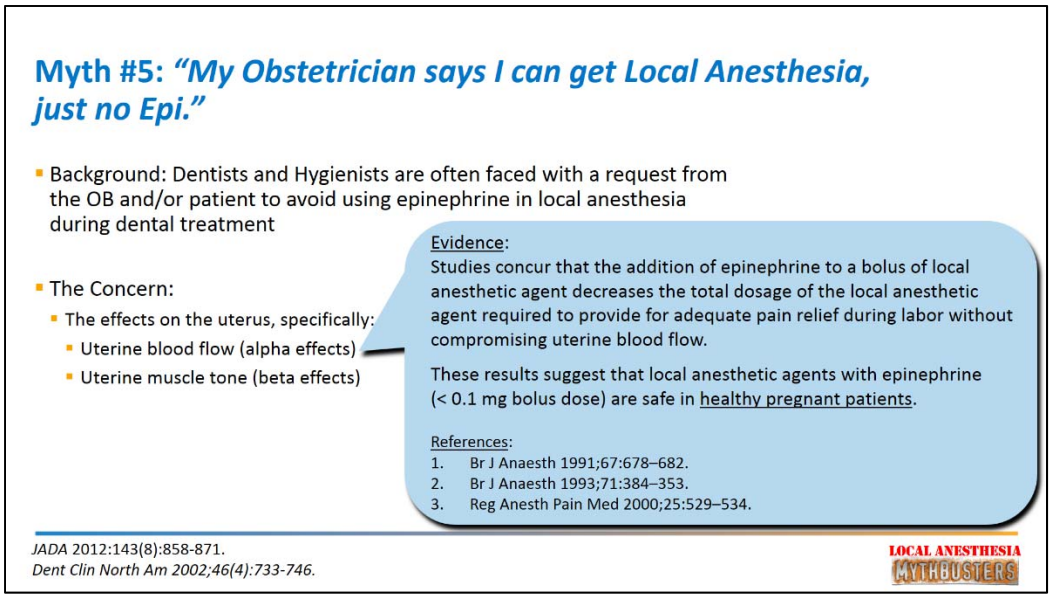
- Medication use during pregnancy is common; two out of every three women take prescription medications during pregnancy. (*American Journal of Obstetrics and Gynecology* 2004; 191:398-407.)
- Medication use during pregnancy still causes great anxiety and misunderstanding among both the public and health care professionals.
- The majority of birth defects have an unknown cause, however one early publication estimated that 2-3% of birth defects are thought to be caused by medications taken during pregnancy. (*Teratology* 1973; 7:3-15.)

Local Anesthetics	Pregnancy Category	Safe during Pregnancy?	Safe during breastfeeding?
Articaine	C	Use with Caution	Use with caution
Bupivacaine	C	Use with Caution	Yes
Lidocaine (with or without epinephrine)	B	Yes	Yes
Mepivacaine (with or without levonordefrin)	C	Use with Caution	Yes
Prilocaine	B	Yes	Yes
Benzocaine (topical)	C	Use with caution	Use with caution
Dyclonine (topical)	C	Yes	Yes
Lidocaine (topical)	B	Yes	Yes
Tetracaine (topical)	C	Use with caution	Use with caution

Source: *JADA* 2012:143(8):858-871.

The Concern:
The effects on the uterus, specifically:

- Uterine blood flow (alpha effects)
- Uterine muscle tone (beta effects)



A true contraindication to epinephrine in local anesthetics for pregnant dental patients is if the pregnancy is complicated by hypertension.

References:
Br J Anaesth 1991;67:678–682.
Br J Anaesth 1993;71(3):348–53.

Myth #5: *"My Obstetrician says I can get Local Anesthesia, just no Epi."*

- Background: Dentists and Hygienists are often faced with a request from the OB and/or patient to avoid using epinephrine in local anesthesia during dental treatment
- The Concern:
  - The effects on the uterus, specifically:
    - Uterine blood flow (alpha effects)
    - Uterine muscle tone (beta effects)

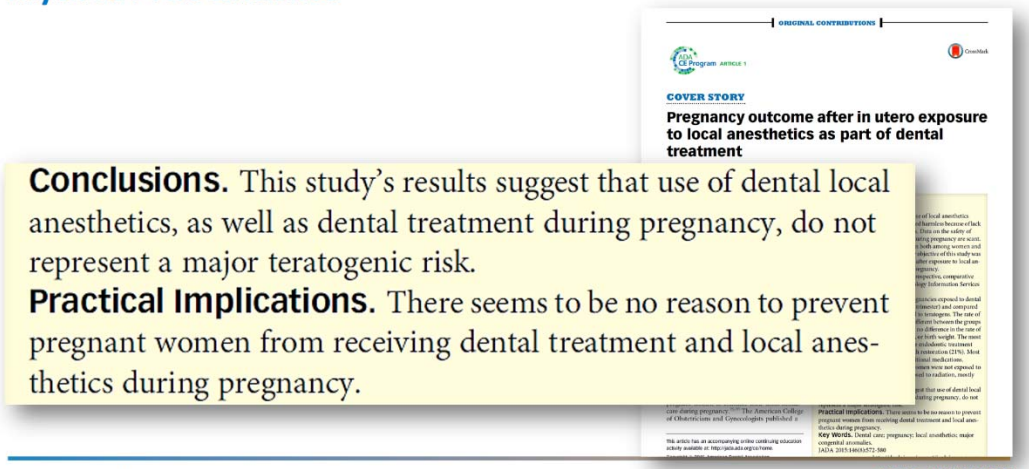
Evidence:
A number of investigators have shown that less than 0.1 mg of epinephrine as a bolus dose prolonged the duration of epidural anesthesia without affecting the duration of labor.
(equivalent to 5 cartridges 1:100,000 epinephrine)

References:
1. Anesth Analg 1987;66:447–451.
2. Anaesthesia 1988;43:100–103.
3. Anesth Analg 1987;66:71–75.
4. Anesth Analg 1984;63:973–979.
5. Anesth Analg 1985;64:585–591.

JADA 2012:143(8):858-871.
Dent Clin North Am 2002;46(4):733-746.

LOCAL ANESTHESIA MYTHBUSTERS

Myth #5: The Evidence


ORIGINAL CONTRIBUTIONS

COVER STORY

Pregnancy outcome after in utero exposure to local anesthetics as part of dental treatment

Conclusions. This study's results suggest that use of dental local anesthetics, as well as dental treatment during pregnancy, do not represent a major teratogenic risk.

Practical Implications. There seems to be no reason to prevent pregnant women from receiving dental treatment and local anesthetics during pregnancy.

JADA 2015:146(8):572-580.

LOCAL ANESTHESIA MYTHBUSTERS

The Verdict…

This myth is BUSTED. Your safest choices if a local anesthetic is indicated for a pregnant patient are:

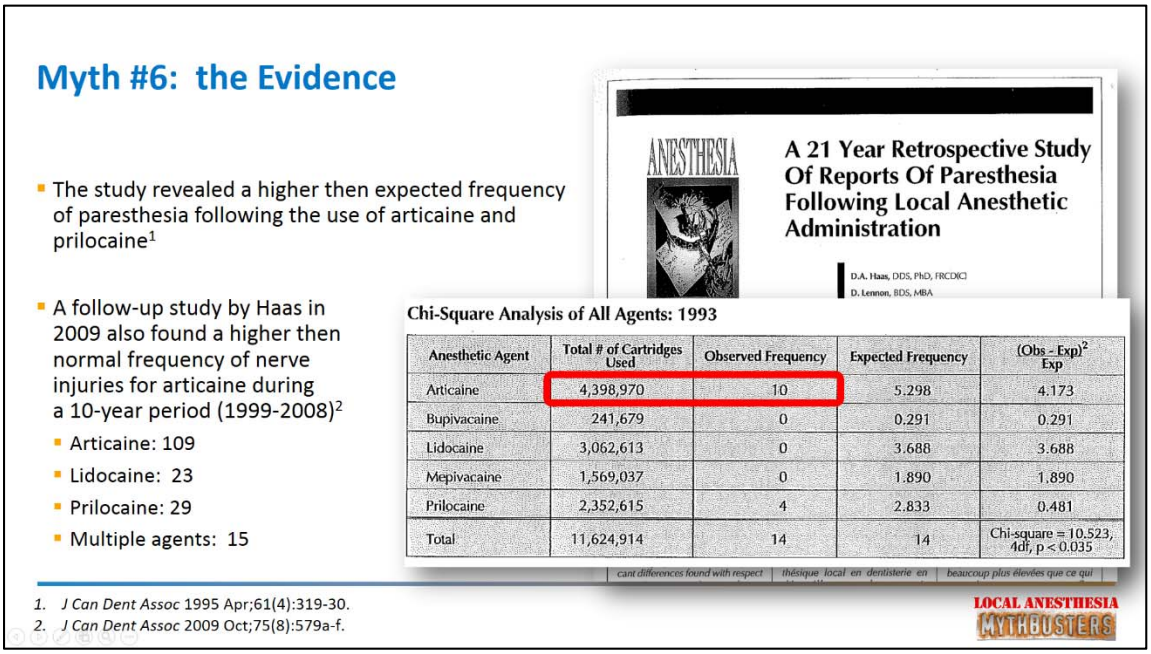
Lidocaine with or without EPI
Prilocaine with or without EPI

Myth #6: "I don't use articaine for blocks because it causes paresthesia."

- A paresthesia as an abnormal sensation, such as of burning, pricking, tickling, or tingling
- Paresthesias are one of the more general groupings of nerve disorders known as neuropathies
- Paresthesias may manifest as total loss of sensation (ie, anesthesia), burning or tingling feelings (ie, dysesthesia), pain in response to a normally nonnoxious stimulus (ie, allodynia), or increased pain in response to all stimuli (ie, hyperesthesia)

Articaine important dates: (Malamed SF. Articaine 30 years later. Oral Health. Feb 2016)

- 1969: Developed in Germany
- Entered clinical use
  - 1976: Germany
  - 1983: Canada
  - 1998: United Kingdom
  - 2000: United States
  - 2005: Australia



Myth #6: The Evidence

- Examined nerve injuries in Denmark from 1997-2004
- 56 total
- Highlighted the lingual nerve as a high risk area for nerve injury

Int. J. Oral Maxillofac. Surg. 2006; 35: 437–443
doi:10.1016/j.ijom.2005.10.004, available online at http://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

Clinical Paper
Oral Medicine

Nerve injury caused by mandibular block analgesia

S. Hillerup[1], R. Jensen[2]
[1]Department of Oral and Maxillofacial Surgery, Rigshospitalet, University of Copenhagen, Denmark; [2]Danish Headache Center, Department of Neurology, Glostrup Hospital, University of Copenhagen, Denmark

	Inferior alveolar nerve	Lingual nerve	Sum *N* (%)
Articaine 4%	5	24	29 (54%)
Prilocaine 3%	4	6	10 (19%)
Lidocaine 2%	3	7	10 (19%)
Mepivacaine 3%	0	4	4 (7%)
Mepivacaine 3% + Articaine 4%	0	1	1 (2%)
Number of nerve injuries	12	42	54 (100%)

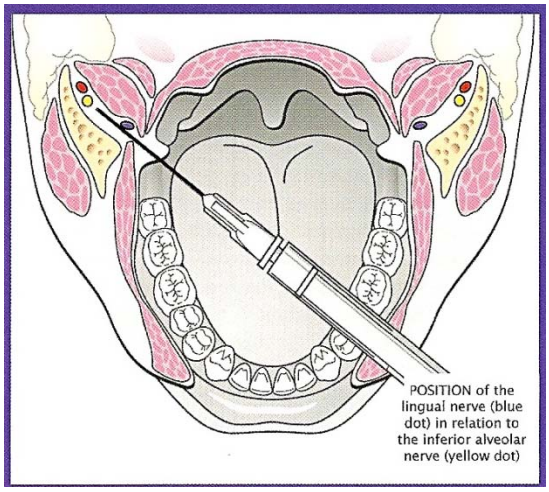
Int J Oral Maxillofac Surg 2006;35:437-443.

LOCAL ANESTHESIA MYTHBUSTERS

A 2003 study showed a range in the number of fascicles present within the lingual nerve, being anywhere from 1 to 8. Of the 12 nerves studied, 4 (33%) had only 1 fascicle

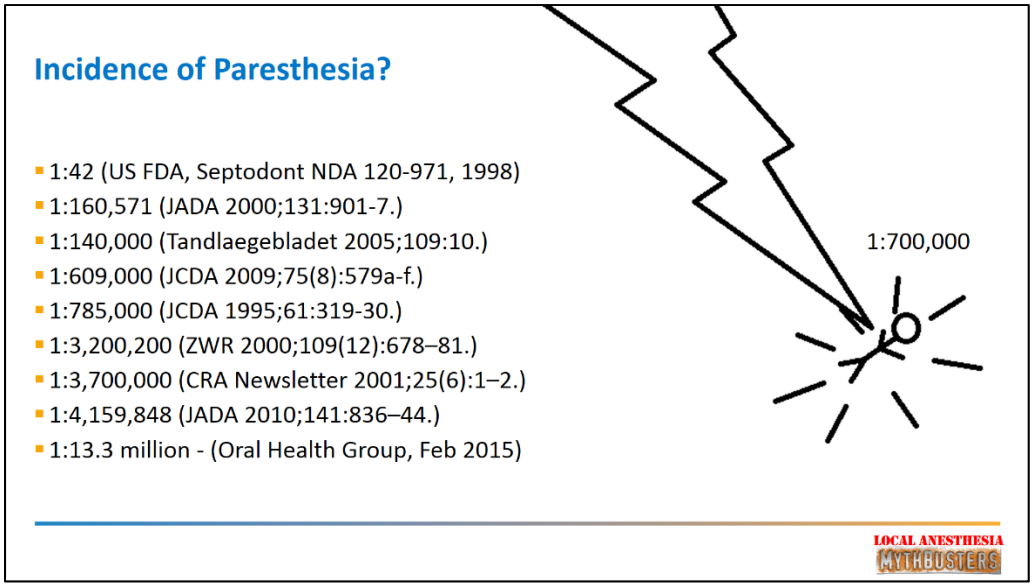
The investigators speculated that a unifascicular nerve may be injured more easily than a multifascicular one

To date, this seems to be the most plausible explanation for the finding of the predilection of the lingual nerve for permanent paresthesia



References:

- *JADA* 2003;134(2):195–199.
- *Team Work* 2009;2(2):28-34.

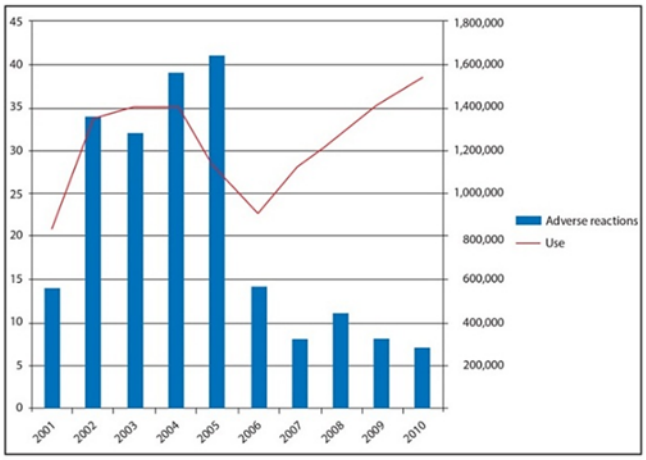


- Let's keep it real… PARESTHESIA IS A RARE EVENT!
- The mechanism is UNCLEAR
- Factors thought to be involved with Paresthesia:
    - Direct needle trauma
    - Intra-neural hematoma
    - Extra-neural hematoma
    - Edema (extra- and intra-neural)
    - Chemical neurotoxicity of articaine

"Weber Effect":

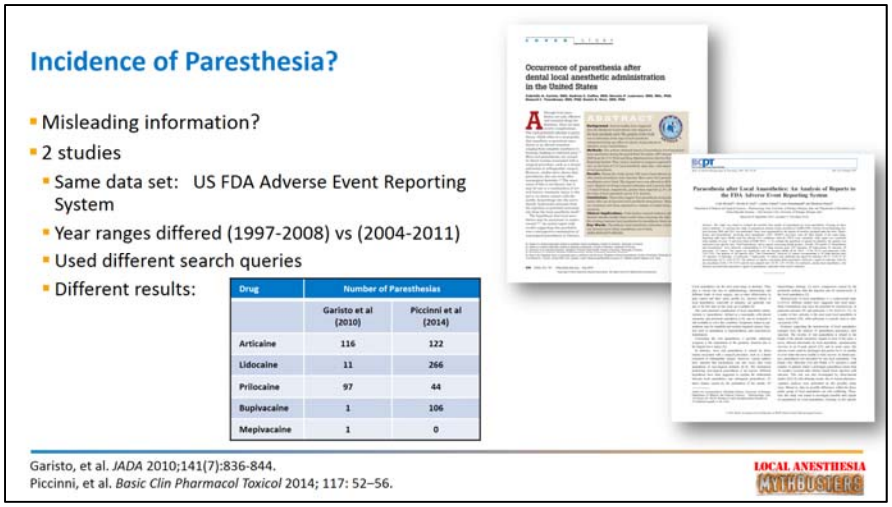
Where a new product when introduced to the marketplace is subject to a closer level of scrutiny by users than more traditional, well-known products

At some point you see… fewer reports of adverse events despite increased use



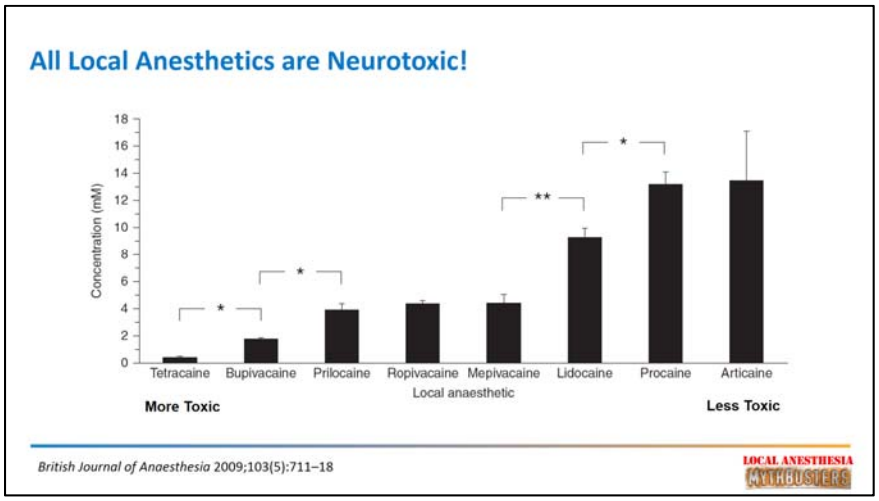
Reference:

- *Dent Update* 2015; 42: 88–93.
- *JADA* 2010;141(7):836-844.
- www.OralHealthGroup.com



Neurotoxicity?

- Articaine may be less neurotoxic then other local anesthetics
- 4% versus 2%?



The Verdict… UNCLEAR

- Despite reports about paresthesias and articaine – the data linking the two is largely anecdotal and of insufficient quality to make clinical guidelines - retrospective and biased
- Controlled studies are needed!
- Clinical neurotoxicity of 2% vs. 4% solutions is unclear and unproven
- The risks ratios are all over the map!
- Change technique rather than local anesthetic?

So what should I do?

- Use articaine for IANB injections
- If not convinced, use lidocaine (buffered?)
- Or, use lidocaine for IANB, use articaine via buccal infiltration
- Or, use articaine only on the maxilla or not at all

Donaldson D, Orr J. A comparison of the effectiveness of nitrous oxide scavenging devices. J Can Dent Assoc. 1989 Jul;55(7):535-7.

Donaldson D, Quarnstrom F, Jastak JT. The combined effect of nitrous oxide and oxygen and electrical stimulation during restorative dental treatment. J Am Dent Assoc. 1989 Jun;118(6):733-6.

Doran M, Rassam SS, Jones LM, Underhill S. Toxicity after intermittent inhalation of nitrous oxide for analgesia. BMJ. 2004 Jun 5;328(7452):1364-5.

Fujinaga M, Mazze RI, Baden JM,et al. Anesthesiology. 1988 Sep;69(3):401-4.

Gillman M. Nitrous oxide/oxygen conscious sedation without adequate scavenging. SADJ. 2005 Mar;60(2):68, 77

Hong K, Trudell JR, O'Neil JR, Cohen EN. Metabolism of nitrous oxide by human and rat intestinal contents. Anesthesiology. 1980 Jan;52(1):16-9.

Iwata K, O'Keefe GB, Karanas A. Neurologic problems associated with chronic nitrous oxide abuse in a non-healthcare worker. Am J Med Sci. 2001 Sep;322(3):173-4.

Jastak JT, Donaldson D. Nitrous oxide. Anesth Prog. 1991 Jul-Oct;38(4-5):142-53.

Jevtovic-Todorovic V, Beals J, Benshoff N, Olney JW. Prolonged exposure to inhalational anesthetic nitrous oxide kills neurons in adult rat brain.
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Lane GA, Nahrwold ML, Tait AR, Taylor-Busch M, Cohen PJ, Beaudoin AR. Anesthetics as teratogens: nitrous oxide is fetotoxic, xenon is not. Science. 1980 Nov 21;210(4472):899-901

Louis-Ferdinand RT. Myelotoxic, neurotoxic and reproductive adverse effects of nitrous oxide. Adverse Drug React Toxicol Rev. 1994 Winter;13(4):193-206.

Maze M, Fujinaga M. Recent advances in understanding the actions and toxicity of nitrous oxide. Anaesthesia. 2000 Apr;55(4):311-4.

Nahrwold ML, Cohen PJ. Additive effect of nitrous oxide and halothane on mitochondrial function. Anesthesiology. 1973 Nov;39(5):534-6.

Quarnstrom F. Nitrous oxide analgesia. What is a safe level of exposure for the dental staff?
Dent Today. 2002 Apr;21(4):104-9.

Shah RM, Donaldson D. The effects of nitrous oxide on the developing hamster embryos.
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Weber NC, Toma O, Awan S, Frassdorf J, Preckel B, Schlack W. Effects of nitrous oxide on the rat heart in vivo: another inhalational anesthetic that preconditions the heart? Anesthesiology. 2005 Dec;103(6):1174-82.

Weimann J. Toxicity of nitrous oxide. Best Pract Res Clin Anaesthesiol. 2003 Mar;17(1):47-61.

Other Notes or Questions to Ask:

Nitrous Oxide Administration – Rapid Induction Technique

Rapid Induction Technique

- To be used where the patient's normal percentage of nitrous oxide has been established.

Establish Tidal Volume

Rapid Induction Technique

- Establish Tidal Volume with 100% Oxygen
- Increase flow to 10 litres per minute

  (Collapse Bag)

- Increase % of Nitrous to Maximum (70%)

Rapid Induction Technique

- Have Patient Take 3 deep breaths

  (Collapse Bag)

- Reduce % to Normal Required Level e.g. 35%
- Sedation Should Occur after a few breaths

Alternate Rapid Induction Technique

- Establish tidal volume
- Take patient to usual end-point for sedation e.g. 35-40%
- Wait for few minutes

What's in Your Emergency Kit and Why

What is an Emergency? Any condition which if left untreated may lead to patient morbidity or mortality.

Why Should You Care About Emergencies?

- In a survey of 2,704 dentists throughout North America, a total of 13,836 emergencies occurring within a 10-year period was reported.
- None of these emergencies were truly dental emergencies. They were potentially life-threatening medical problems that patients developed while they were in a dental office.
- Almost all medical emergencies that occur in a dental office are fear-related.
- If fear and apprehension are reduced, the chances of having a medical emergency are also reduced.
- Three-quarters of all of these medical emergencies developed as sequelae of pain (i.e., inadequate local anesthesia), the dentist's failure to recognize and treat a patient's fear of dental care, or both.

Malamed SF. Managing medical emergencies. JADA 1993;124(8):40-53.

Medical emergencies reported by 2,704 dentists.*

EMERGENCY SITUATION	NO. (%) OF EMERGENCIES REPORTED†
Syncope‡	4,161 (30.1)
Mild Allergic Reaction	2,583 (18.7)
Postural Hypotension	2,475 (17.9)
Hyperventilation‡	1,326 (9.6)
Insulin Shock (Hypoglycemia)	709 (5.1)
Angina Pectoris‡	644 (4.6)
Seizures‡	644 (4.6)
Asthmatic Attack (Bronchospasm)‡	385 (2.8)
Local Anesthetic Overdose	204 (1.5)
Myocardial Infarction	187 (1.4)
Anaphylactic Reaction	169 (1.2)
Cardiac Arrest	148 (1.1)

* Source: Malamed.[1]
† A few emergencies with low numbers were omitted from the table.
‡ Emergencies that potentially are stress related.

How Do You Manage Emergencies?

The Best Preparation is Prevention:

- Know your patient: get a complete medical and pharmacological history.
- Review any problem areas.
- Take training.
  - Practice
  - Practice
  - Practice
- Manual - Simple with flow charts.
- Emergency Kit.
- Equipment - Less is better.
- Phone – Cell.
- Medication - Only what you will use and are comfortable using . . .

Other Notes or Questions to Ask:

Stress-Reduction Protocol

- ✓ Recognize medical risk.
- ✓ Consult patient's physician(s).
- ✓ Pharmacosedation, as indicated.
- ✓ Short appointments.
- ✓ Morning appointments.
- ✓ Excellent intraoperative pain control.
- ✓ Minimize waiting room time.
- ✓ Excellent post-operative pain control.

Rosenberg, M. Preparing for Medical Emergencies: Essential Drugs and Equipment for the Dental Office. J Am Dent Assoc 2010; 141;14S-19S.

Suggested basic emergency drugs for the general dental office.

INDICATION	DRUG	ACTION	ADMINISTRATION
Bronchospasm (Severe Allergic Reaction)	Epinephrine	α- and β-adrenergic receptor agonist	Autoinjectors or preloaded syringes, ampules; 1:1,000 solution subcutaneously, intramuscularly or sublingually; adults, 0.3 milligram; children, 0.15 mg
Mild Allergic Reaction	Diphenhydramine	Histamine blocker	50 mg intramuscularly; 25 to 50 mg orally every three to four hours
Angina	Nitroglycerin	Vasodilator	Sublingual tablet: one every five minutes up to three doses; translingual spray: one spray every five minutes up to three times
Bronchospasm (Mild Asthma)	Bronchodilator such as albuterol	Selective β_2- adrenergic receptor agonist	Two or three inhalations every one to two minutes, up to three times if needed
Bronchospasm (Severe Asthma)	Epinephrine	α- and β-adrenergic receptor agonist (bronchodilator)	Autoinjectors or preloaded syringes, ampules; 1:1,000 solution subcutaneously, intramuscularly or sublingually; adults, 0.3 mg; children, 0.15 mg
Hypoglycemia	Glucose, as in orange juice	Antihypoglycemic	If the patient is conscious, ingest
Myocardial Infarction	Aspirin	Antiplatelet	One full-strength tablet (165-325 mg) chewed and swallowed
Almost Anything	Oxygen	Respiratory Support	Ad Lib

#1: Epinephrine 1:1,000 Injection

- ✓ Uses: to reverse hypotension, bronchospasm, and laryngeal edema that result from an acute anaphylactoid type reaction. Also used to reduce bronchospasm resulting from an acute asthmatic episode that is refractory to inhaler therapy.

- ✓ Pharmacology: Causes vasoconstriction that in turn increases blood pressure, heart rate, and force of contraction. Also causes bronchial dilatation. Reduces the release of histamine. Can be ineffective if the patient is taking beta-blocker.

- ✓ Adverse Effects:
  a) Cardiovascular: Tachycardia, Tachyarrhythmia's, and hypertension.
  b) Central Nervous System: Agitation, headache, and tremors.
  c) Endocrine System: Increased blood glucose.
  d) Pregnant Female: Can decrease placental blood flow.

- ✓ Dose: Supplied in vials, ampules, or pre-loaded syringes in concentration of 1:1000 (1mg/mL). IV give 0.5-2.0mg (0.5ml-2.0ml) depending on severity of hypotension, titrate to effect repeat in 2 minutes if needed. IM give 0.3mg (0.3ml) repeat in 10-20 minutes as needed.

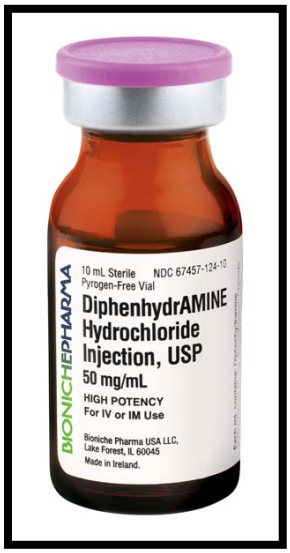
Other Notes or Questions to Ask:

#1: EpiPen Instead??

Stecher D, Bulloch B, Sales J, et al. Epinephrine Auto-injectors: Is Needle Length Adequate for Delivery of Epinephrine Intramuscularly? Pediatrics 2009;124;65-70

CONCLUSION: The needle on epinephrine auto-injectors is not long enough to reach the muscle in a significant number of children. Increasing the needle length on the auto-injectors would increase the likelihood that more children receive epinephrine by the recommended intramuscular route.

#2: Diphenhydramine (Benedryl) 50mg Injection



- ✓ Uses: To reduce the affects of histamine release that is associated with allergic reactions, anaphylaxis, and acute asthma attack precipitated by exogenous causes.
- ✓ Pharmacology: An antihistamine that blocks the release of histamine in the body. It does not prevent the action of the histamine once released and thus must be given quickly. Prevents histamine responses suck as bronchospasm, hypotension, rash, and edema.
- ✓ Adverse Effects:
  1. Cardiovascular: Tachycardia.
  2. Central Nervous System: CNS depression (sedative effects including drowsiness, lethargy, and mental confusion).
  3. Gastrointestinal: Xerostomia.
- ✓ Dose: 50-100mg IM or IV. For mild cases of pruritis, urticaria, or erythema an oral dose of 50mg every 6 hours can be used.

#3: Nitroglycerin

If patients have a history of angina and you are considering giving them their nitro or yours (from the EMG kit), what MUST you know?

- For *Viagra* and *Levitra*, at least 24 hours should have elapsed since the last dose of a PDE5 inhibitor.
- For *Cialis*, allow at least 48 hours before using nitrates.

J Am Coll Cardiol 1999; 33:273-82
J Am Coll Cardiol 2003; 42:1855-60

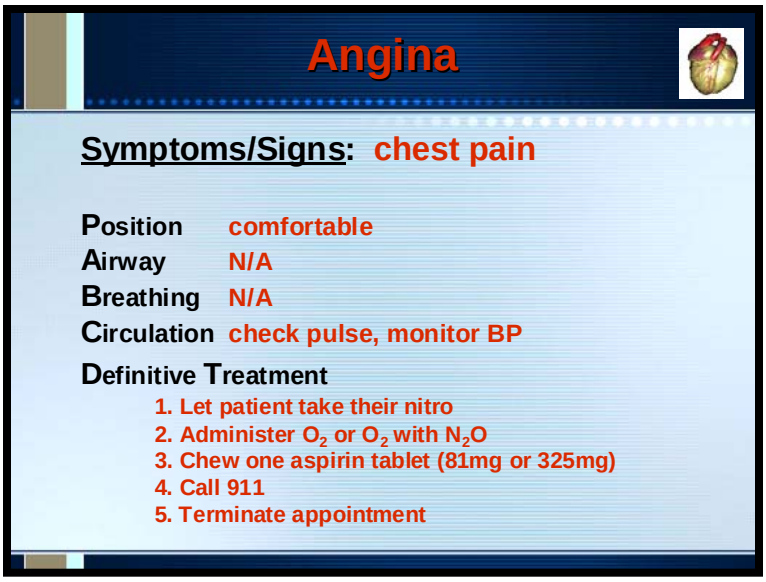
- ✓ Uses: Used to relieve or eliminate chest pain associated with angina pectoris, to differentiate between angina and a myocardial infarction.
- ✓ Pharmacology: A coronary and peripheral vasodilator and as such helps increase the flow of oxygenated blood to the heart muscle.

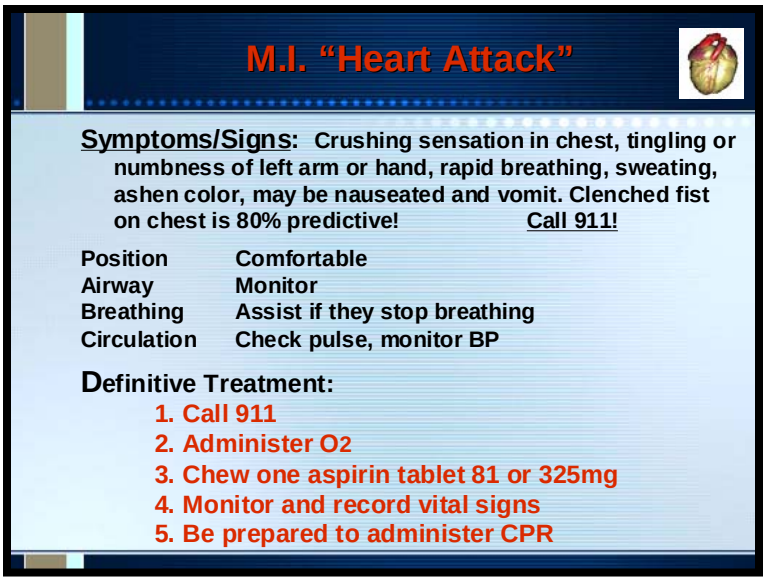
Other Notes or Questions to Ask:

- ✓ It also causes venous pooling of blood decreasing venous return to the heart thus improving the pumping efficiency of the heart. Because of this improved efficiency myocardial oxygen demand is decreased.

- ✓ Adverse Effects:
  a) Cardiovascular: Rapid heart rate, facial flushing, and orthostatic (Postural) hypotension.
  b) Central Nervous System: Dizziness and headache.

- ✓ Dose:
  a) Tablet: 1 tablet sublingually repeat after 2 minutes if no relief up to 3 doses.
  b) Metered Dose Spray: 1 spray sublingually repeat after 2 minutes if no relief up to 3 doses.





Called "remote ischemic preconditioning," the procedure developed by Toronto's Hospital for Sick Children was found to significantly limit the amount of damage to the heart muscle caused by a blockage in a cardiac blood vessel.

Ischemic preconditioning involves using the device to interrupt blood flow in the arm, off and on over a period of 35 to 40 minutes: the cuff is inflated for five minutes, then deflated for five minutes, with the procedure being repeated consecutively four times.

http://www.cbc.ca/health/story/2010/02/26/heart-attack-blood-pressure-cuff.html#ixzz0gfLoHNbP

#4: Oxygen

Bag-Valve Concentrations:

- Without oxygen - 21%
- With oxygen, no reservoir - 60%
- With oxygen and reservoir - 90 to 95%
- With demand valve attachment - 100%

Other Notes or Questions to Ask:

M.I. "Heart Attack"

Women are different !

Most frequent symptoms:

Prodromal	During Acute MI
71% unusual fatigue	58% short of breath
48% sleep disturbance	55% weakness
42% shortness of breath	43% unusual fatigue
39% indigestion	39% cold sweat
35% anxiety	39% dizziness
> 30% had chest pain	

43% did not have chest pain during Acute MI
95% knew their symptoms were new and different a month or more prior to the Acute MI.

M.I. "Heart Attack"

1. Call 911
2. M.O.N.A
   - Morphine for pain control
   - O_2 Administration
   - Nitroglycerine 1 dose q5min to max of 3. Ask both men and women if they have had Viagra in the last 24 hr. No nitro if yes as it can lead to dangerously low BP.
   - ASA Chew one tablet (81mg or 325mg). This is as important as nitroglycerin.
3. Be prepared to administer CPR.
4. The sooner they get to the hospital the better for dilation of vessels or fibrinolysis.

#5: Aspirin (for Acute Coronary Syndromes)

- ✓ Pharmacology: Irreversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, via acetylation, which results in decreased formation of prostaglandin precursors; irreversibly inhibits formation of prostaglandin derivative, thromboxane A2, via acetylation of platelet cyclooxygenase, thus inhibiting platelet aggregation; has antipyretic, analgesic, and anti-inflammatory properties.

- ✓ Uses: Treatment of mild-to-moderate pain, inflammation, and fever; prevention and treatment of myocardial infarction (MI), acute ischemic stroke, and transient ischemic episodes; management of rheumatoid arthritis, rheumatic fever, osteoarthritis, and gout (high dose); adjunctive therapy in revascularization procedures (coronary artery bypass graft [CABG], percutaneous transluminal coronary angioplasty [PTCA], carotid endarterectomy), stent implantation.

- ✓ Precautions:
  - Bleeding disorders: Use with caution in patients with platelet and bleeding disorders.
  - Dehydration: Use with caution in patients with dehydration.
  - Ethanol use: Heavy ethanol use (>3 drinks/day) can increase bleeding risks.
  - Gastrointestinal disease: Use with caution in patients with erosive gastritis or peptic ulcer disease.
  - Hepatic impairment: Avoid use in severe hepatic failure.
  - Renal impairment: Use with caution in patients with mild-to-moderate renal impairment (only at high dosages); avoid in severe impairment.

#6: Albuterol Inhaler (bronchodilator)

- ✓ Uses: Used during acute asthma or Anaphylaxis to reduce or control bronchospasm.

- ✓ Pharmacology: A β_2-adrenergic drug that relaxes the bronchial smooth muscle. It has rapid onset and duration of action of up to 6 hours. Also reduces the stimulation of mucous production.

Other Notes or Questions to Ask:

✓ Albuterol and Beta-Blockers tend to inhibit each other.

✓ Adverse Effects:
Should be used with caution in patients with cardiovascular disorders especially coronary artery disease, arrhythmias, and hypertension.

✓ Dose:
2 puffs every 2 minutes to a maximum of 20 puffs. Hold inhaler about 2 inches from mouth. Have patient take two deep breaths and then exhale forcefully. Dispense one puff on slow deep inhalation. Hold breath for 10 seconds and repeat.

#7: Glucose (for hypoglycemia)

✓ Symptoms:
- Appears confused
- Cool, moist skin
- May be hungry
- May seem "drunk" but not alcohol breath odor
- Slurred speech

– If patient becomes unconscious or does not respond readily after sugar/carbohydrate administration, activate EMS. They will give IV treatment.
– Never give unconscious patient anything orally!

Should I Have Other Drugs?

- Midazolam (Versed®)?
- Flumazenil (Romazicon®)?
- Nitrous Oxide?
- Corticosteroids?
- Aromatic Ammonia?
- Naloxone (Narcan®)?

Do Not Get Yourself Locked Into A Serious Drug Collection!

Other Notes or Questions to Ask:

Better Medicine, Better Dentistry: Appropriate Analgesic Prescribing

Classification of Pain: Most Americans experience three or four types of pain per year. There are over 50 million Americans partially or totally disable by pain with an annual cost to the system of $336 billion (*American Academy of Pain Medicine 2015*). The goals of therapy for pain are to decrease the intensity, increase physical activity, appropriate use of medications, regulation of sleep patterns and moods, as well as reestablishing work habits.

Acute pain has a treatment goal of a cure. Most of the symptoms associated with chronic pain are not present. **Chronic pain** often results in dependence and tolerance, psychological component is a major problem, a significant environmental change and family involvement and insomnia. The treatment goal for chronic pain is rehabilitation, not a cure.

Treatment may involve one or more of the following **pain management options**: Physical, Psychological or Pharmacological. Physical management involves exercise, cutaneous stimulation, repositioning and counterstimulation (acupuncture). Psychological management involves relaxation techniques, patient education support groups and meditation. Pharmacological management involves **non-opioid analgesics**, **opioid analgesics** and **co-analgesic medications**.

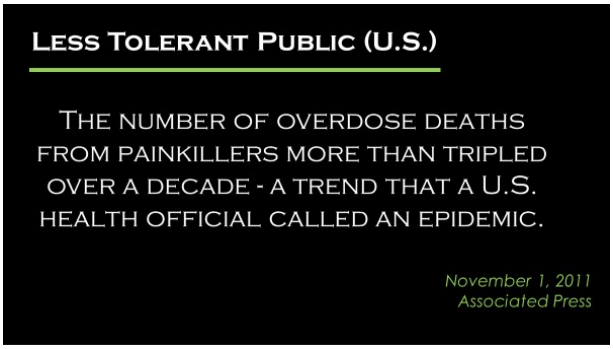
Dentists write approximately 20 million prescriptions for analgesics annually in U.S.. The major indication in dentistry is to manage postoperative pain, requiring a prescription of only a few days duration. Most often the challenge is to give high enough doses over a few short days to cover the inflammatory period, without putting the patient at risk of adverse sequelae. Although the cornerstone of these prescriptions focus on the non-opioid analgesics and opioid analgesics, it is important to remember that most pain of dental origin is due to the inflammatory process, which is why non-steroidal antiinflammatory drugs (NSAIDs) make the most sense for treatment. Opioid-based medications act centrally and do not have antiinflammatory properties.

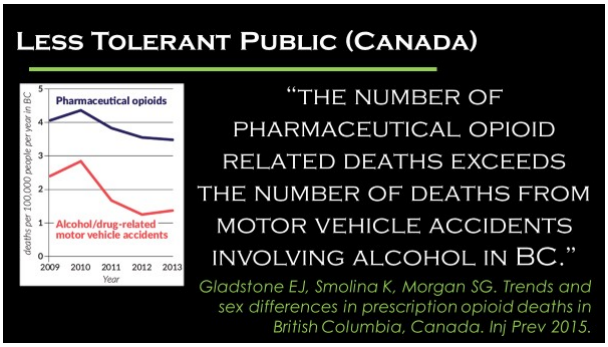
The Drug Armamentarium: We will discuss pharmacological pain management by dividing the discussion into Peripheral Analgesics (non-opioid analgesics), Central Analgesics (opioid analgesics), Co-Analgesics and Local Anesthetics.

Analgesics used for Postoperative Dental Pain

Acetaminophen - Tylenol
Aspirin - Aspirin (various)
Ibuprofen - Advil, Motrin, Nuprin
Flurbiprofen - Ansaid
Diflunisal - Dolobid
Naproxen - Naprosyn, Aleve
Ketorolac - Toradol
Ketoprofen - Orudis
Etodolac – Lodine
Codeine - Codeine (in various)
Oxycodone - Percocet, Percodan
Meperidine - Demerol
Pentazocine - Talwin
Hydrocodone - Lortab, Vicodin
Dihydrocodeine - Synalgos-DC
~~Propoxyphene - Darvon~~

*** Propoxyphene-containing products such as Darvon were removed from the US market in 2010 .**

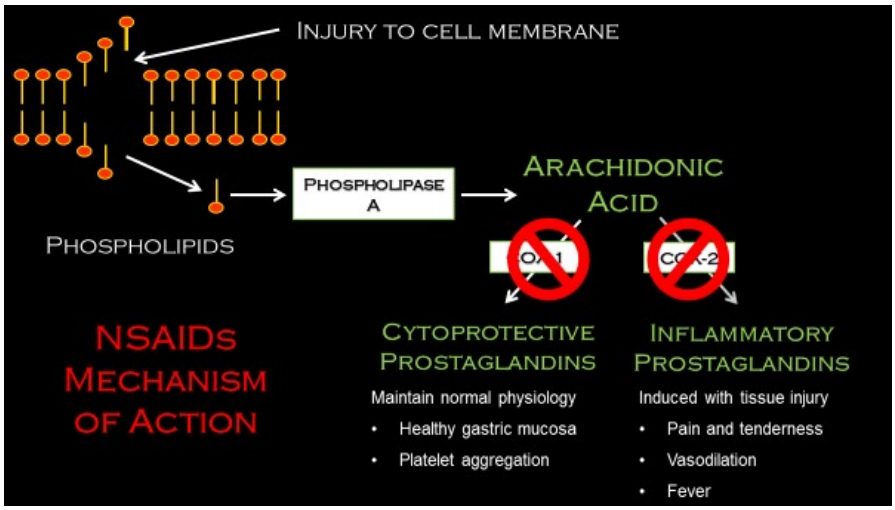




Other Notes or Questions to Ask:

Peripheral Analgesics: non-Opioid Analgesics

Acetaminophen may be the most ubiquitous medication in this category. It is comparable to ASA and NSAIDs in analgesic and antipyretic activity, but only has a weak anti-inflammatory activity. In patients who are maintained on blood thinners or have a history of bleeding complications, acetaminophen dose offer one major advantage over ASA and NSAIDs as it has a minimal antiplatelet effect and does not injure the gastric mucosa. Adult dosages range from 325mg to 1000mg administered three to four times per day, with a maximum daily dose of no more than 4.0 grams (4000mg) to avoid hepatotoxicity. In those patients at risk for liver problems (e.g., Chronic alcoholics, hepatitis patients), the maximum recommended dose should not exceed 2.0 grams (2000mg). The pediatric dose of acetaminophen is 10-15 mg/kg/dose orally every 4-6 hrs (maximum 5 doses/day).



Prostaglandins generated during tissue damage direct some actions of inflammation: fever, pain and vasodilation. Inhibiting prostaglandin synthesis leads to a decrease in this response, which led to the advent of **NSAIDs** as an alternative to acetaminophen.

The mechanism of action of NSAIDs is to block the conversion of arachidonic acid to prostaglandins. Arachidonic acid is a by-product of the breakdown of injured cell membrane phospholipids by the enzyme phospholipase. Non-selective **COX inhibitors** not only block the inflammatory prostanoids which produce pain, tenderness, vasodilation and fever, but they also inhibit the cytoprotective prostanoids that maintain a normal gastric mucosa and normal platelet aggregation. **COX-2** inhibitors only block the inflammatory prostanoids and do not effect the protective gastric mucosa and hemostasis.

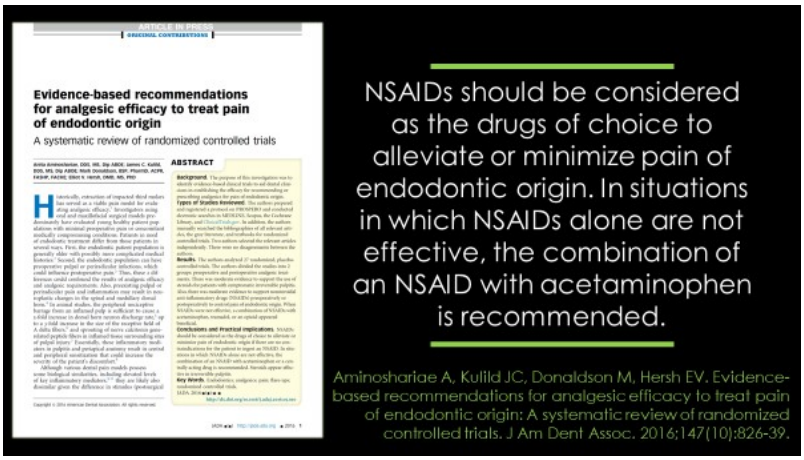
There are a plethora of NSAIDs on the market and rather than reviewing each one individually, some key points should be stressed. Be familiar with at least three agents and their usual dosing regimens and maximum daily dosages. Some examples are:

- Ibuprofen (Motrin) 400-600 mg four times a day (max daily dose is 2400mg)
- Diclofenac (Voltaren) 25-50mg two or three times a day (max daily dose is 200mg)
- Naproxen (Naprosyn) 250-500mg two or three times a day (max daily dose is 1500mg)

Aminoshariae A, Kulild JC, Donaldson M, Hersh EV. Evidence-based recommendations for analgesic efficacy to treat pain of endodontic origin: A systematic review of randomized controlled trials. J Am Dent Assoc. 2016;147(10):826-39

Other Notes or Questions to Ask:

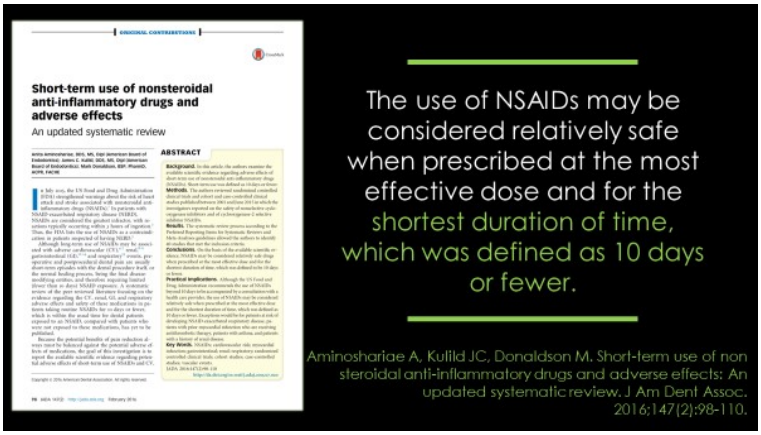
NSAID Mortality: Fortunately or unfortunately, many of these medications are now available without a prescription, which may give prescribers the false sense that they are completely "safe" (without adverse sequelae). In fact, **16,500 people die in US each year due to NSAID complications**. The mechanism of action of NSAID's is to inhibit both COX-1 and COX-2 (cyclooxygenase isoenzymes) which are responsible for the production of prostaglandins: the mediators of inflammation. Some of these prostaglandins are cytoprotective, however, as part of the body's natural homeostatic process. By non-specifically inhibiting both isoenzymes, NSAIDs have been associated with an increased rate of gastritis, gastric erosion and even ulceration.



Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. N Engl J Med. 1999 Jun 17;340(24):1888-99.

Baseline Risk of Peptic Ulceration: Hospitalization risk due to peptic ulceration is about 0.2% per year in non-NSAID users. The risk increase to 0.8% in patients currently taking NSAIDs and GI hemorrhage is the most common presentation. The risk is higher in men than women. The range of risk is from 0.5% to 1.7% depending on dose, drug and duration.

NSAID Prescribing: Not all NSAIDs are created equally. The risk of GI toxicity varies from: **ibuprofen → ASA → diclofenac → naproxen → indomethacin → piroxicam → ketoprofen→ ketorolac.** When you prescribe NSAIDs, do so only to patients who do not respond to acetaminophen. Select the NSAID with the lowest toxicity and prescribe the lowest possible dose for the shortest duration of time. The use of NSAIDs may be considered relatively safe when prescribed at the most effective dose and for the shortest duration of time, which was defined as 10 days or fewer



Aminoshariae A, Kulild JC, Donaldson M. Short-term use of nonsteroidal anti-inflammatory drugs and adverse effects: An updated systematic review. J Am Dent Assoc. 2016;147(2):98-110

<u>COX - 2 INHIBITORS</u>:

COX-2 Inhibitors were developed to decrease GI effects of NSAIDS. Older NSAID's inhibit both COX-1 and COX-2 prostanoids. COX-1 is responsible for protecting the GI mucosa (cytoprotective). COX-2 is responsible for inflammatory mediation. COX-2 selectivity increases from:

ketorolac → ketoprofen → indomethacin → ASA → ibuprofen→ piroxicam → diclofenac → celecoxib→ meloxicam

Other Notes or Questions to Ask:

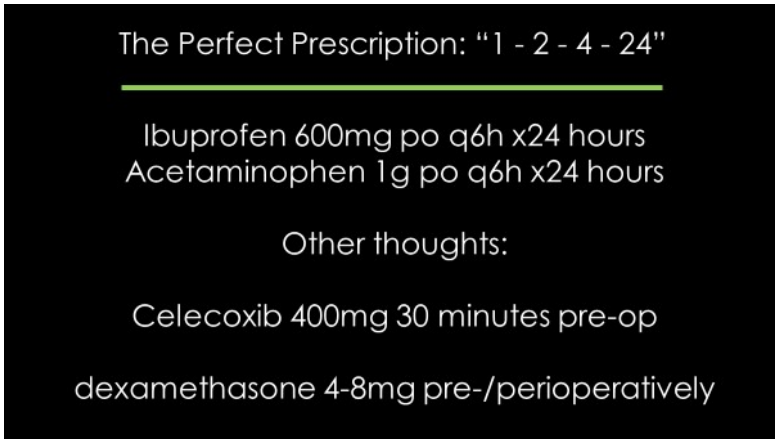
When rofecoxib (Vioxx) was available, it was the most selective of available NSAIDs (>50-fold potency for COX-2 over COX-1) and was is twice as selective as celecoxib. Vioxx was unfortunately removed from the US market in 2004. The COX-2 inhibitor seem to be equally effective as the NSAIDs. There seems to be no difference in overall adverse effects. There seems to be no difference in real effects. In these 3 studies no dyspeptic symptom differences were noted. However, there was an absolute difference in endoscopically proven ulcer of 10 – 25% decrease. Also note that where COX-2 inhibitors were used, they had no effect on platelets.

Differences between the COX-2s: If a patient has a sulfa allergy you should avoid the Celecoxib/Valdecoxib medications. There still is a question if one should not prescribe COX-2s if an aspirin allergy exists. Recognize that Celecoxib has a slightly slower onset of activity. Obviously, with the removal of **Vioxx** & **Bextra** from the market, adverse effects can not be ruled out!

When to use a COX-2? Use a COX-2 inhibitor if other less expensive NSAIDs have been shown to be ineffective or not tolerated. Use a COX-2 inhibitor if cost is not an issue. Use a COX-2 inhibitor if your patient is controlled on a blood thinner like coumadin. Use a COX-2 inhibitor if you are planning to use misoprostol with an NSAIDS.

These newer medications can be up to ten times more expense than the traditional NSAIDs, and should generally be reserved for those patients who have failed prior treatment with NSAIDs, or if they are controlled on a blood thinner like coumadin.

- ~~rofecoxib (Vioxx) 50mg QD~~
- ~~veldecoxib (Bextra) 10mg QD~~
- celecoxib (Celebrex) 200mg BID



Donaldson M and Goodchild JH. Appropriate analgesic prescribing for the general dentist. Gen Dent 2010; 58(4):291-7.

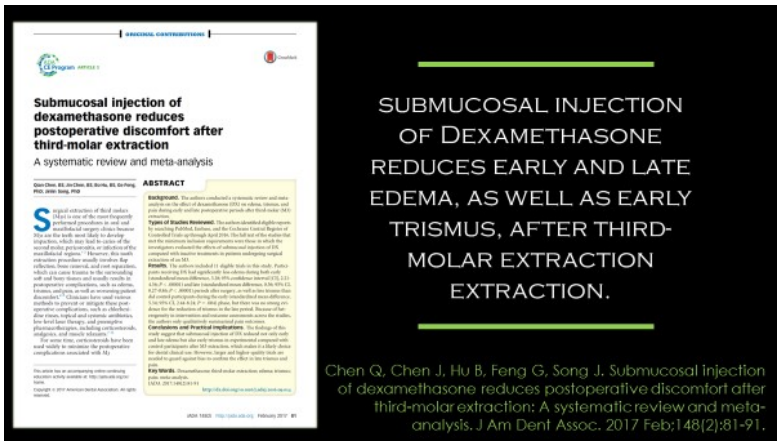
Becker DE. Managing Acute and Postoperative Dental Pain. Anesth Prog 2010; 57(10): 67-79.

Gordon J. Christensen: Clinicians Report. Pain Meds: What Works? February 2015.

What about the use of Steroids?

Dexamethasone is a glucocorticoid (FDA approved 1958). Supplied as Tablets (0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, 6 mg); Injection (4mg/mL, 10mg/mL, 20mg/mL); Elixir (0.5 mg/5 mL)

Plasma Half-Life: 3-5 hours
Duration of Action: 2.5-6 days to treat pain, swelling and trismus.



Chen Q, Chen J, Hu B, Feng G, Song J. Submucosal injection of dexamethasone reduces postoperative discomfort after third-molar extraction: A systematic review and meta-analysis. J Am Dent Assoc. 2017 Feb;148(2):81-91.

Other Notes or Questions to Ask:

Opioid-Based Analgesics: Central Analgesics

When to use them: Opioids such as morphine, meperidine, hydromorphone, fentanyl and others should not always be considered the drugs of choice for all postoperative analgesia cases. They act centrally, have no effect on the inflammatory process, and are associated with adverse sequelae in many patients ranging from constipation to more acute narcotizing effects.

How to use them: Having said this, they may still have a role in pain management, as interpatient response to any type of drug therapy is highly variable. The same general prescribing guidelines described above hold true for opioid-based analgesics: be familiar with at least three agents and their usual dosing regimens. Be aware of drug interactions with other CNS depressant. Most drug interaction software available today does not recognize the obvious interactions between opioid and benzodiazepines.

Pain Control: the site of action for the opioid narcotics is in the brain stem. Where as NSAIDs and COX-2 inhibitors work at the site of injury.

Maximum daily dosages do not readily apply to these agents and it may be more clinically useful to be aware of the minimum effective dosages and potential equiefficacious dosing when switching between agents.

In trying to achieve the best of both worlds there are several combination products which incorporate either acetaminophen or an NSAID with an opioid-based analgesic (eg. Percocet, Vicodin, and Vicoprofen). The practitioner should still decide if an opioid-based analgesic is appropriate therapy for the particular case, and they should also be aware of the maximum recommended daily doses of acetaminophen or the NSAID being used in the combination product. This is especially important in those patients who are ordered both Tylenol and Percocet, for example (since they both contain acetaminophen).

Drug	Route	Equianalgesic dose	Duration of Action (hr)
Morphine	IM, SC PO	10mg 30-60mg	4-6 4-6
Meperidine	IM, SC PO	100mg 200mg	2-4 2-4
Hydromorphone	IM, SC PO	2mg 6-8mg	4-5 4-5
Oxycodone/ Hydrocodone	PO	30mg	3-4
Codeine	IM PO	60mg 120-180mg	4-6 4-6
Fentanyl	IM Transderm	0.1-0.2mg 25μg/hr	Very short 72

Equianalgesic dosing tables are available for opioid-based analgesic medications, which aid in prescribing or changing a patient's regimen to a different agent, but it must be stressed that these are only guidelines and are usually based on single-dose studies in healthy individuals. Some examples of these guidelines are shown below:

Other Notes or Questions to Ask:

1 x Tylenol #3	**=**	**300mg Acetaminophen + 30mg Codeine**
2 x Tylenol #3	**=**	**10mg oral Morphine**
1 x Vicodin	**=**	**500mg Acetaminophen + 5mg Hydrocodone**
2 x Vicodin	**=**	**10mg oral Morphine**
1 x Tylenol #3	**=**	**1 x Vicodin tablet**

Morphine: Morphine is still the gold standard in pain control because of the wide rage of dosage forms and low cost. There are even sustained release preparations that allow a dose once every 12 hours. These sustained release medications are MS Contin, M-Eslon, Kadian. In the elderly M=Eslon offers some advantages because the capsule can be pulled apart and contents mixed as long as the granules are not crushed.

Hydromorphone (Dilaudid): This drug is excellent for patients allergic to morphine. Dilaudid SR (sustained release) comes in 3, 6 and 12mg capsules. The dosing is every 12 hours and the capsules can be opened. This drug is also effective when morphine tolerance develops. You should switch from morphine to hydromorphone when morphine doses needed by the patient are increasing rapidly. In the non-narcotic naïve patient the ratio is about 5:1.

Meperidine (Demerol): There is no advantage with Demerol over morphine for chronic pain. This drug has a shorter half-life, but its active metabolite (normeperidine) has an extended half-life of 8-12 hours. Meperidine may accumulate with repeated administration leading to CNS stimulation that manifests itself as agitation, irritability, nervousness, tremors, twitching and seizures. Since this drug is eliminated by the kidneys, patients with decreased renal function are more susceptible to CNS stimulation from repeated administration. A major contraindication is in patient receiving MAO inhibitors. This may cause severe respiratory depression, coma and decrease in blood pressure.

Fentanyl (Duragesic): Fentanyl can be useful if enteral narcotics are not an option. The dose is limited to 25, 50 75 and 100mcg increments. One need to wait 24 hours to evaluate the effectiveness for pain control. This drug is not for acute pain! It may take 6 days after increasing the dose before a new steady state level is achieved. If the drug is administered in a patch, the serum concentration will take approximately 17 hours to re-equilibrate.

Other Opioids: Codeine is a relatively weak analgesic. Oxycodone and Hydrocodone usually are in combination products such as Percocet and Vicodin. Be aware that because of these combination products a toxicity level may be reached if doses of acetaminophen exceed 4 grams per day.

Constipation: … the eleventh commandment*? **"the hand that writes the narcotic order shall write the laxative order!"***

Other medications for pain: TCA Antidepressants such as amitriptyline, nortriptyline and imipramine are examples. **SSRI** (Selective Serotonin Reuptake Inhibitors) Antidepressants such as fluoxetine (Prozac), sertraline (Zoloft), citalopram (Celexa) and escitalopram (Lexapro) are examples. **Anticonvulsants** such as valproate (Epival), carbamazepine (Tegretol) and gabapentin (Neurontin) are examples. Finally **Glucocorticoids** such as dexamethasone, prednisone, methylprednisolone and hydrocortisone are examples.

Efficacy of Tramadol: Ibuprofen>Tramadol/Acetaminophen>acetaminophen>Tramadol>Placebo

Other Notes or Questions to Ask: